EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	GPA.clm. and hG-CSF.clm.	US-PGPUB	OR	OFF	2006/06/19 14:06
L2	2	dahiyat.in. and hG-CSF	US-PGPUB; USPAT	OR	OFF	2006/06/19 14:10
L3	3	(dahiyat.in. or luo.in.) and hG-CSF	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	OFF	2006/06/19 14:11
L4	202	G-CSF same substitution$2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/06/19 14:13
L5	38	G-CSF same substitution$2 same ("17" or "28")	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2006/06/19 14:14

Welcome to DIALOG

Dialog level 05.11.05D

Logon file001 19jun06 13:23:00
? b 411;set files biotech
    19jun06 13:23:09 User219511 Session D647.2
      $0.00 0.102 DialUnits File410
  $0.00 Estimated cost File410
  $0.03 TELNET
  $0.03 Estimated cost this search
  $0.44 Estimated total session cost 0.220 DialUnits
File 411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2006 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
  You have 25 files in your file list.
  (To see banners, use SHOW FILES command)
? s (G-CSF or hG-CSF) and (17 or 28) and substitution?

Your SELECT statement is:
  s (G-CSF or hG-CSF) and (17 or 28) and substitution?

      Items File
      ----- ----
        2 34: SciSearch(R) Cited Ref Sci_1990-2006/Jun W2

  1 file has one or more items; file list includes 25 files.

? s (G-CSF or hG-CSF) and (17 or 28)

Your SELECT statement is:
  s (G-CSF or hG-CSF) and (17 or 28)

      Items File
      ----- ----
      237 5: Biosis Previews(R)_1969-2006/Jun W2
      381 34: SciSearch(R) Cited Ref Sci_1990-2006/Jun W2
       88 71: ELSEVIER BIOBASE_1994-2006/Jun W3
      142 94: JICST-EPlus_1985-2006/Mar W3
        2 135: NewsRx Weekly Reports_1995-2006/Jun W2
        2 144: Pascal_1973-2006/May W4
        2 155: MEDLINE(R)_1951-2006/Jun 19
        3 434: SciSearch(R) Cited Ref Sci_1974-1989/Dec

  8 files have one or more items; file list includes 25 files.

? save temp; b 5;exs;t s1/7/1-237;bye
Temp SearchSave "TH26084288" stored
    19jun06 13:24:19 User219511 Session D647.3
      $2.12 0.800 DialUnits File411
  $2.12 Estimated cost File411
  $0.53 TELNET
  $2.65 Estimated cost this search
  $3.09 Estimated total session cost 1.019 DialUnits

File 5:Biosis Previews(R) 1969-2006/Jun W2
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    Set Items Description
    --- ----- -----------
Executing TH26084288
HILIGHT set on as '%'
      1194 G-CSF
         4 HG-CSF
    415970 17
    276752 28
S1 237 (G-CSF OR HG-CSF) AND (17 OR 28)

1/7/1
DIALOG(R)File 5:Biosis Previews(R)
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0015882234 BIOSIS NO.: 200600227629
ESHAP plus fixed dose G-CSF as autologous peripheral blood stem cell mobilization regimen in patients with relapsed or refractory diffuse large cell and Hodgkin's lymphoma: a single institution result of 127 patients
AUTHOR: Akhtar S (Reprint); Tbakhi A; Humaidan H; El Weshi A; Rahal M; Maghfoor I
AUTHOR ADDRESS: King Faisal Specialist Hosp and Res Ctr, POB 3354, Riyadh 11211, Saudi Arabia**Saudi Arabia
AUTHOR E-MAIL ADDRESS: sakhtar@kfshrc.edu.sa
JOURNAL: Bone Marrow Transplantation 37 (3): p277-282 FEB 2006 2006
ISSN: 0268-3369
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: From 1996 to November 2004, 131 consecutive patients with relapsed or refractory diffuse large cell lymphoma (DLCL) and Hodgkin's lymphoma (HD) received ESHAP as mobilization chemotherapy before autologous peripheral blood stemcell transplant (ASCT). Patients received fixed dose G-CSF 300 mu g SC bid starting 24 - 36 h after finishing mobilizing ESHAP. In all, four patients failed mobilization and are excluded. Characteristics of 127 patients: 68 males: 59 females. DLCL 49: HD 78. Initial stage I: II: III: IV: unknown was 15: 34: 33: 42: 3. Median age at ASCT 26 years. Median prior chemotherapy cycles were six {<6 (%17% patients), 6 - 8 (90 patients), 48 (20 patients)}. Median ESHAP cycle used as mobilizer was third. Patients required 1, 2, 3, 4 apheresis were 93: 25: 8: 1. Median total CD34+ cells/kg collected were 6.9 x 10(6) (DLCL 5.%17% x 10(6) and HD 7.6 x 10(6)), patients weighing <= 70 kg (93 patients) 6.54 x 10(6) and 470 kg (34 patients) 7.44 x 10(6) (P = 0.59), one apheresis (93 patients) 8.6 x 10(6)/ kg and >1 apheresis (34 patients) 4.5 x 10(6) (P = 0.001). We conclude that ESHAP and G-CSF 300 mu g SC bid is an effective mobilizing regimen even in patients 470 kg and most patients require only 1 - 2 apheresis.

1/7/2
DIALOG(R)File 5:Biosis Previews(R)
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0015874849 BIOSIS NO.: 200600220244
Conference of the Italian-Association-for-the-Study-of-the-Liver, Naples, ITALY, October 26 -%28%, 2005
AUTHOR: Anonymous
JOURNAL: Digestive and Liver Disease 37 (10): pA55-A69 OCT 2005 2005
CONFERENCE/MEETING: Conference of the Italian-Association-for-the-Study-of-the-Liver Naples, ITALY October 26 -28, 2005; 20051026
SPONSOR: Italian Assoc Study Liver
ISSN: 1590-8658
DOCUMENT TYPE: Meeting
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This meeting contains 42 abstracts from oral and poster presentations, written in English, on the subject of digestive and liver disease. Included are the etiology, pathology and therapy of different liver diseases, efficacy and safety of drug monotherapy or combination therapy, liver transplantation, the effect of viral infection and treatment on the digestive system and diagnostic and surgical techniques.

1/7/3
DIALOG(R)File 5:Biosis Previews(R)

0015865884 BIOSIS NO.: 200600211279
Treatment with combination peginterferon alfa-2b and ribavirin of recurrent hepatitis C in liver transplant recipients nonresponsive to interferon alfa-2b and ribavirin
AUTHOR: Samanta Arun; Mandalapu Amarvani; Fisher Adrian; Wilson Dorian; de la Torre Andrew; Klein Kenneth M; Koneru Barburao
JOURNAL: Gastroenterology 128 (4, Suppl. 2): pA455-A456 APR 2005 2005
CONFERENCE/MEETING: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week Chicago, IL, USA May 14 -19, 2005; 20050514
SPONSOR: Amer Gastroenterol Assoc
ISSN: 0016-5085
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hepatitis C recurs in virtually all liver transplant recipients, runs an aggressive course and causes graft dysfunction and loss. Treatment with interferon and ribavirin has not impacted the disease progression. Outcome data on pegylated interferon plus ribavirin treatment of nonresponders to interferon plus ribavirin for post transplant hepatitis C is scarce and end point of treatment not well defined.Aim: To study treatment efficacy of peginterferon afla-2b plus ribavirin for post-transplant recurrent hepatitis C nonresponsive to interferon alfa-2b plus ribavirin.Methods: Twenty-six patients with post transplant hepatitis C recurrence, unresponsive to interferon alfa 2b and ribavirin were treated with pegimerferon alfa-2bplus ribavirin. Criteria for hepatitis C recurrence included elevated ALT and AST, circulating HCV-RNA, histologic features of hepatitis and absence of rejection. Patients were treated with weekly pegylated interferon alfa 2b 1.5 mcg/kg and daily ribavirin starting at 400 mg (increased to 1000 mg). Erythropoietin and G-CSF were given when required. Results: Mean age was 52.4 +/- 7.5 years 85% were male, Twenty-three patients (88.5%) completed treatment for 24 to 60 weeks and three (11.5%) stopped medication for drug intolerance. Tolerated dose for peginterferon was 88 +/- 42 mcg/week (range 32-240 mcg/week) and for ribavirin was 600 +/- 200 mg/day (range 400-1000 mg/day). Dose interruption for peginterferon occurred in 12 (46% and 15 (57%) required erythropoietin and/or G-CSF. At end of treatment, ALT, AST and HCV-RNA (57 +/- %28% IU, 60 +/- 40 IU and 500,000 +/- 200,000 copies/ml respectively) decreased significantly ($p < 0.05$) from pretreatment values (109 +/- 82 IU, 90 +/- 70 IU, and 4,000,000 6,000,000 copies/ml respectively). Intent-to-treat analysis showed end of treatment biochemical response (normalization of transaminases) in 10 patients (38%) and HCV-RNA clearance in 5 (19%). Sustained response (undetectable HCV-RNA at six months after treatment) occurred in one (4%).Conclusions: Treatment of post transplant hepatitis C recurrence with peginterferon alfa-2b plus ribavirin for 24-60 weeks in nonresponders to interferon alfa 2b plus ribavirin achieves viral decrease in many patients with improvement in transaminases at the end of treatment. However, sustained viral clearance is achieved in a few (4%). Dose reduction or interruption for drug intolerance limits therapy in post transplant population, Longer duration of therapy may prove beneficial.

1/7/4
DIALOG(R)File 5:Biosis Previews(R)

0015860854 BIOSIS NO.: 200600206249
Addition of cladribine to induction/consolidation regimen does not impair peripheral blood stem cell mobilization and bone marrow harvest for autotransplantation in acute myeloid leukemia patients
AUTHOR: Holowiecki J (Reprint); Grosicki S; Sadus-Wojciechowska M; Kachel L ; Hellmann A; Mital A; Skotnicki A B; Piatkowska-Jakubas B; Jedrzejczak W W; Paluszewska M; Wach M; Marianska B; Wrzesien-Kus A; Krawczyk-Kulis M; Wojnar J
AUTHOR ADDRESS: L Warynski Silesian Med Acad, Univ Dept Hematol and BMT, Polish Adult Leukemia Grp, Reymonta St 8, PL-40029 Katowice, Poland**
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AUTHOR E-MAIL ADDRESS: holow@mail.slam.katowice.pl
JOURNAL: Transplantation Proceedings 37 (10): p4482-4487 DEC 2005 2005
ISSN: 0041-1345
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. The previous study by the Polish Adult Leukemia Group has demonstrated that addition of cladribine to standard DNR+AraC induction potentiates the antileukemic activity. The goal of this study was to compare the efficacy of bone marrow or peripheral blood hematopoietic cell collection in patients who obtained remission after daunorubicine plus cytarabine induction with cladribine (DAC-7) or without addition of cladribine (DA-7) in preparation for autotransplantation.Patients and Methods. Sixty-six patients aged 41 years (range, %17%-58 years) were included in this study: 33 cases in the DAC-7 and 33 in the DA-7 arm. Hematopoietic cells were collected from the bone marrow (ABMT, n = 29) or from the peripheral blood (ABCT, n = 37) using cytopheresis after administration of AraC (2 x 2 g/m(2)) on days 1, 3, 5 and subsequent G-CSF (10 mu g/kg) from day 7 as mobilization therapy.Results. The numbers of harvested CD34(+) cells were similar in the DAC-7 and DA-7 pretreated patients both after harvesting from peripheral blood (2.55 x 10(6)/kg vs 2.5 x 10(6)/kg) and from bone marrow (1.62 x 10(6)/kg vs 1.55 x 10(6)/kg), respectively. The proportion of patients with sufficient material for autologous bone marrow transplantation was higher in the DAC-7 compared with the DA-7 arm. All patients engrafted; hematopoietic recovery was similar in both subgroups.Conclusion. Addition of cladribine to a standard DA induction does not impair the harvesting of hematopoietic cells and their engraftment after autotransplantation.

1/7/5
DIALOG(R)File 5:Biosis Previews(R)

0015839892 BIOSIS NO.: 200600185287
Effect of AMD3100 on T lymphocyte subpopulations in apheresis products of patients undergoing autologous hematopoietic stem cell transplantation for non Hodgkin lymphoma
AUTHOR: Holtan Shernan G (Reprint); Porrata Luis F; Inwards David J; Ansell Stephen A; Padley Douglas J; Micallef Ivana N; Litzow Mark R; Johnston Patrick B; Hayman Suzanne R; Kumar Shaji K; Gertz Morie A; Lacy Martha Q; Dispenzieri Angela; Gastineau Dennis A; Teferi Ayalew; Elliot Michelle; Hogan William J; Markovic Svetomir N
AUTHOR ADDRESS: Mayo Clin, Coll Med, Dept Internal Med, Div Hematol, Rochester, MN USA**USA
JOURNAL: Blood 106 (11, Part 1): p819A NOV 16 2005 2005
CONFERENCE/MEETING: 47th Annual Meeting of the American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005; 20051210
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: AMD3100, a CXCR4 receptor antagonist, has been studied as a stem cell mobilization agent for the purpose of autologous stem cell transplantation (ASCT) in hematologic malignancies. Lymphocyte subset analysis of peripheral blood in patients treated with AMD3100 has been studied in healthy volunteers. To date, no reports exist describing the lymphocyte subsets of the autograft in patients undergoing AMD3100 stem cell mobilization for the purposes of ASCT in non-Hodgkin lymphoma (NHL). Considering our prior work demonstrating the significant impact of autograft lymphocyte content on clinical outcomes of patients undergoing ASCT for NHL we set out to profile autograft lymphocyte subsets of patients undergoing mobilization with AMD3100. Using flow cytometry, we analyzed aliquots of apheresis products in 7 patients with NHL undergoing AHSCT who received AMD3100 in addition to G-CSF as a part of their

mobilization regimen. These results were compared to 29 patients with NHL who had undergone stem cell mobilization with G-CSF alone. There were no significant differences between these two groups of patients in terms of sex, age, performance status, histology, LDH, and number of pretransplant chemotherapeutic regimens. CD34+ cells collected at apheresis did not differ significantly between the groups, However, compared with G-CSF alone, patients that received AMD3100 had an approximate 5-fold increase in CD4+ cells (0.62 x 10(9) cells/kg vs. 0.12 x 10(9) cells/kg, p = 0.0004), a 3.5-fold increase in the absolute number of autograft CD3+ cells (1.21 x 10(9) cells/kg vs. 0.33 x 10(9) cells/kg, p = 0.0017), and a 2.5-fold increase in CD8+ cells (0.48 x 10(9) cells/kg vs 0.19 x 10(9) cells/kg, p = 0.2 15). A significant increase was also noted in CD4+25+ cell compartment (0.%17% x 10(9) cells/kg vs. 0.006 x 10(9) cells/kg, p = 0.0001). No significant difference was noted in the absolute number of autograft CD 16+56+ NK cells. Finally, an increase in the autograft total absolute lymphocyte count (41.6 x 10(9) cells/kg vs. 2.88 x 10(9) cells/kg, p < 0.001) as well as peripheral blood absolute lymphocyte count at day 15 after AHSCT was observed in those patients who had received AMD3100 (0.79 x 10(9) cellAg vs. 0.58 x 10(9) cells/kg, p = 0.04). The increased lymphocyte content ofthe autograft (total and subset) would suggest the potential of positive impact on clinical outcomes in patients mobilized with AMD3 100. Indeed, none of the patients who received AMD3100 had relapsed disease at one year post-transplant (although two of these patients are currently 9 months and 11 months post-transplant respectively), whereas 10 of the 29 control patients had relapsed disease at one year. Further studies are necessary to confirm these observations and ascertain their clinical significance.

1/7/6
DIALOG(R)File 5:Biosis Previews(R)

0015839705 BIOSIS NO.: 200600185100
Hematopoietic cell transplantation-specific comorbidity index to predict non-relapse mortality and survival after allografting.
AUTHOR: Kato Ruri (Reprint); Fukuda Takahiro; Usui Eiji; Yamasaki Satoshi; Maruyama Dai; Morita Yuriko; Kim Sung-Won; Mori Shin-ichiro; Tanosaki Ryuji; Tajima Kinuko; Heike Yuji; Makimoto Atsushi; Tobinai Kensei; Takaue Yoichi
AUTHOR ADDRESS: Natl Canc Ctr, Hematopoiet Cell Transplantat Unit, Tokyo, Japan**Japan
JOURNAL: Blood 106 (11, Part 1): p766A-767A NOV 16 2005 2005
CONFERENCE/MEETING: 47th Annual Meeting of the American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005; 20051210
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pre-transplant comorbidity can affect the outcome of allogeneic hematopoietic cell transplantation (HCT). The Seattle group recently proposed a new HCT-specific comorbidity index (HCT-CI) which was based on the Charlson Comorbidity Index (Blood, prepublished online, June 30, 2005).To validate this scoring system, we retrospectively reviewed the medical records of 315 patients with hematologic malignancies who underwent allogeneic HCT after fludarabine-based reduced-intensity (n = 160) or conventional (n = 155) conditioning at our center between 2000 and 2004. The median age of the patients was 46 (range, 1-68) years. The diagnoses included acute myeloid leukemia or myelodysplastic syndrome (n=153), chronic myelogeneous leukemia (n=30), acute lymphoblastic leukemia (n=36), lymphoma (n=90), and other hematologic malignancies (n=6). Donors included HLA-matched m=120) or mismatched (n=53) relatives and unrelated volunteers (n=142). Stem cell source was G-CSF-mobilized peripheral blood stein cell (n=169), bone marrow (n=117), or cord blood (n=29). We did not include the pulmonary function test results due to our inconsistency with the test.The HCT-CI captured 45% of patients with scores > 0 (score 1, n=71; score 2, n=22; score 3, n=27; score 4, n=15: score > 4, n=6). The capture rate of HCT-CI in patients who received reduced-intensity conditioning was higher than that in those who received conventional conditioning (51% vs 38%). The involved organ systems included hepatic (n=68), recent infection (n=38), prior malignancies (n= %17%), cardiac (n=16), renal (n=11), metabolic (n=11), psychiatric (n=11), pulmonary (n=8), and gastrointestinal (n=4) abnormalities. The Kaplan-Meier estimate of overall survival was significantly different among risk groups stratified according to HCT-CI (Figure 1, p < 0.0001). In Cox proportional hazard models, a higher HCT-CI score, disease risk, and transplant from donors other than HLA-matched relatives were associated with poor overall survival. A higher HCT-CI score, greater patient age, and transplant from donors other than HLA-matched relatives were associated with a significantly increased risk for non-relapse mortality.In conclusion, the new HCT-CI using pre-transplant variables was the most significant predictor of non-relapse mortality and survival after allografting. Our validation study suggests that this index will be a useful tool for future use in clinical trials and standard practice.[GRAPHICS]

1/7/7
DIALOG(R)File 5:Biosis Previews(R)

0015839645 BIOSIS NO.: 200600185040
Computed tomography (CT) scan response stability and gallium scan evaluation as on-treatment prognostic parameters to tailor treatment intensity of newly diagnosed Hodgkin's lymphoma (HL). A prospective phase II study.
AUTHOR: Russo Filippo (Reprint); Svanera Gino; Della Cioppa Paola; Corazzelli Gaetano; Frigeri Ferdinando; Capobianco Gaetana; LaStoria Secondo; Pinto Antonio
AUTHOR ADDRESS: Natl Canc Inst, Oncohematol Unit, Naples, Italy**Italy
JOURNAL: Blood 106 (11, Part 1): p749A-750A NOV 16 2005 2005
CONFERENCE/MEETING: 47th Annual Meeting of the American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005; 20051210
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To improve ABVD results we first developed a protocol which adds G-CSF to the standard ABVD treatment. From March 1997 to May 2004 69 patients with HL were treated with ABVD+G-CSF and 22 with a standard ABVD. Recently we designed a new dose-dense and dose-intensity ABVD scheme (escABVD-21) for advanced HL; in this new schedule the adriamycin was escalated from 25 to 35 mg/m2 (cycles 1,2,3,4) and the intercycle period was shortened from %28% to 21 days (for all 6 cycles); primary G-CSF was administered from d3 to d8 and drugs were delivered at d10 and d21 of every cycle. From June 2004, 19 patients were treated with this protocol.Relative dose-intensity (RDI) was calculated for any of these 110 newly diagnosed HL patients treated with ABVD. The results were also compared with a historical group of 70 patients who had undergone hybrid MOPP/ABVD.HL patients received from 4 to 8 cycles of CT +/- IF-RT. Patients were divided in 4 groups according to the RDI. The first group included 20 (11 %) pts with RDI less than 0.80; the 2nd group, 64 (36%) pts with RDI values between 0.80 and 0.95, the 3rd group, 74 (42%) pts with RDI values between 0.96 and 1.10 and, finally, the 4th group included pis with RDI values of more than 1.10.In Tab 2 we report the CR, EFS and OS rates according to the 4 levels of RDI. Figures I shows EFS curve according to Kaplan-Meyer.Response and survival rates of groups 1,2,3 and 4 were: 50%vs91% vs 97% vs 100%, for The best progression rates of CR, EFS and OS were seen inpatients with RDI > 1.10. In particular, the new dose-dense and dose-intensity escABVD-21 protocol seems very promising in terms of complete response and toxicity profile: 19/19 pis (100%) obtained an early CR; (PET negative at the end of the 2nd cycle), and, as on 8th August 2005, all these 19 patients were disease-free. The dose-escalation of adriamycin and the close-density of the schedule were

well-tolerated; toxicity was mild.These results show that subptimal RDI may compromise outcomes proportionally to the level of RDI reduction. On the contrary, Primary G-CSF permits to deliver dose-dense and dose intense schedules such as escABVD-21 maintaining the same profile of toxicity of standard ABVD, higher RDI levels, and consequently, a significant impact on complete response and survival rates.[GRAPHICS]sis (IPS, age >= 50 ys, elevated ESR, >= 3 or 4 involved regions, extranodal disease, bulky mediastinal mass), no factors significantly worse in group +/- were found, other than the frequency of bulky mediastinal mass (47% vs %17%%). The 2 on-treatment prognostic parameters identified different subgroups of pts that could not have been identified with standard pre-treatment prognostic factors. Consolidation with RT has been avoided, in 50.4% of the pts, with no detrimental effect on the relapse rate. Longer follow-up is needed to evaluate potential benefit of this approach on treatment-related toxicity. Pts with both late improvement of CT and gallium positivity represent a high risk subgroup, for which early intensification of treatment may be considered.

1/7/8
DIALOG(R)File 5:Biosis Previews(R)

0015839642 BIOSIS NO.: 200600185037
Mortality during treatment of patients with advanced Hodgkin's lymphoma undergoing dose escalated BEACOPP chemotherapy: An analysis of the German Hodgkin study group (GHSG).
AUTHOR: Fuchs Michael (Reprint); Franklin Jeremy; Klimm Beate; Josting Andreas; Pfistner Beate; Engert Andreas; Diehl Volker
AUTHOR ADDRESS: Univ Cologne, German Hodgkin Lymphoma Study Grp, Cologne, Germany**Germany
JOURNAL: Blood 106 (11, Part 1): p749A NOV 16 2005 2005
CONFERENCE/MEETING: 47th Annual Meeting of the American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005; 20051210
SPONSOR: Amer Soc Hematol
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: Due to substantial clinical progress over the past decades, the outcome of patients with Hodgkin's Lymphoma (HL) has improved with a long-term disease free survival of nearly 80%. Even patients with advanced-stage HL show a five year freedom from treatment failure (FFTF) of 87% and overall survival (OS) of 91 % when treated with 8 cycles of BEACOPP(escalated) (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbacine, prednisone). However, BEACOPP(escalated) has been associated with some acute and long-term treatment related mortality (TRM). We thus analysed the incidence, clinical features and risk factors for TRM of patients treated with BEACOPP(escalated) in the HD12 multicenter trial of the GHSG performed between 1998 and 2002. The HD12 was conducted for advanced HL patients (Stage IIB with large mediastinal mass and/or extranodal involvement, stage III/IV). All patients received 8 cycles of chemotherapy either 8x BEACOPP(escalated) (Arm A/B) or4xBEACOPP(escalated) +4xBEACOPP(baseline) (Arm C/D)+/-30Gy radiation on bulk and residual tumor.Results: In this study, 43 patients (3.1 %) from a total of 1392 included died from TRM. 5 patients were excluded from this analysis because of various reasons (change of fist-line therapy due to toxicity, TRM in BEACOPP(baseline)) 38 patients were eligible for this analysis. 30 patients (79%) had infectious complications, 6 (16%) cardiac events such as arrhythmia or heart failure, 1 patient died due to bleomycin-related toxicity and 1 case remained unclear. 25 patients (66%) were older than 50 years in contrast to the whole HD12 study population with only %17%% of patients being older than 50. There was no statistical difference between those cases with treatment related mortality and the whole study population in terms of other clinical risk factors such as gender, B-symptoms, extranodal involvement, stage of disease, large mediastinal mass or elevated ESR. There was also no difference between the 4 study arms. Most events occurred during the first 4 courses of BEACOPP(escalated) (79%) with the majority during the first cycle (n = 12; 32%). 23/26 (89%) of patients who died during cycles 2 - 8 had prior WHO grade III/IV leucopenia or infection.Conclusion: Patient age and toxicity in previous cycles are the most obvious risk factors for TRM in patients with advanced HL undergoing BEACOPP(escalated) chemotherapy. In the HD12 study, the use of G-CSF was mandatory and most patients received their treatment on an outpatient basis. Thus, possible measures to reduce toxicity with this treatment include the prophylactic use of antibiotics as well as treating those with risk factors at least for the first course as inpatients.

1/7/9
DIALOG(R)File 5:Biosis Previews(R)

0015839530 BIOSIS NO.: 200600184925
A phase I-II trial of bortezomib (Veleade) (Vc) and oral cyclophosphamide (CY) plus prednisone (P) for relapsed/refractory multiple myeloma (MM).
AUTHOR: Reece Donna E (Reprint); Piza Giovanni; Trudel Suzanne; Chen Christine; Mikhael Joseph R; Stewart A Keith
AUTHOR ADDRESS: Univ Hlth Network, Princess Margaret Hosp, Toronto, ON, Canada**Canada
JOURNAL: Blood 106 (11, Part 1): p718A NOV 16 2005 2005
CONFERENCE/MEETING: 47th Annual Meeting of the American-Society-of-Hematology Atlanta, GA, USA December 10 -13, 2005; 20051210
SPONSOR: Amer Soc Hematol
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DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Abstract
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ABSTRACT: We have previously reported that a simple, well-tolerated regimen of weekly oral CY (500mg) and alternate day prednisone (50-100mg) produced partial responses (PR) in 40% of 56 patients (pts) in relapse after ASCT; median progression-free survival was 18.6 months (Blood 2004; 104[11]: 311b). To build upon these favorable results, we have designed an ongoing phase I-II trial adding Vc to this regimen. CY was given p.o. once weekly on days 1,8,15 and 22 of each %28% day cycle while prednisone was given every other morning. CY was given before Vc on appropriate days. A maximum of 8 cycles was administered. Sixteen pts have been entered so far.Patients characteristics: Median age was 59 (48-74) years; 9 were male. The Ig subtypes were: IgG kappa:lambda = 9:2, IgA kappa:lambda = 1:2; kappa light chain = 2. All had received VAD, i.v. CY (2.5 g/m(2)) + G-CSF mobilization followed by ASCT and 2 had undergone a second ASCT; other prior regimens included melphalan and prednisone in 5 pts, thalidomide in 10, lenalidomide in 1, a-interferon in 3, vaccine therapy in 1 and oral CY + P in 8. The median pretreament beta 2-microglobulin level was 279 (147 - 875) nm/L, albumin 39 (30-42) g/L and creatinine 91 (60-112) umol/L.Three further dose escalations to a maximum Vc dose of 1.5 mg/m(2) days 1,8, and 15 are allowed if dose limiting toxicity does not occur.Toxicities during cycle 1: All Ins have completed cycle 1. Three episodes of grade (gr) 3 sinopulmonary infection occurred during a community outbreak at dose level 1; levofloxacin prophylaxis during the first cycle was added and no further infections during the initial cycle were observed. One pt at dose level 3 experienced transient gr 4 hypophosphatemia which reversed without therapy. At dose level 4, cycle I was interrupted in one pt due to gr 4 leukopenia (gr 3 neutropenia and thrombocytopenia) related to disease, while a second pt developed grade 4 elevation in transaminases which recovered quickly when Vc was held on d 8. Pt accrual continues.Toxicities of subsequent cycles: To date, 47 additional cycles have been given. SAE's consisted of pneumonia during cycle 2 in the same 3 patients with infection during cycle 1 and one of these with progressive disease had another bout during cycle 3. Gr 3 toxicities included anemia in 2 cycles, leucopenia in 2, neutropenia in 4, hypophosphatemia in I and hyperglycemia in 2; reversible gr 4 hypophosphatemia recurred in the pt mentioned above in I other cycle. No

liver or other organ toxicity was observed. Maximum gr of peripheral neuropathy was 1.Responses: Responses were assessed after cycles 2, 4, 6 and 8. Best response included near CR (1), PR (4), MR (4), stable disease (5), progression (1) and too early (1). Two pts have completed all 8 cycles, while 4 have progressed; 10 remain on study.Preliminary Conclusions: 1) Vc can be added to a continuous program of oral CY + P with acceptable hematologic toxicity; 2) no neurotoxicity > gr 1 has been observed; 3) the maximum tolerated dose (MTD) of this combination regimen has not yet been defined; 4) future plans include a randomized National Cancer Institute of Canada trial comparing the the MTD of this combination to Vc in relpased MM pts.

1/7/10
DIALOG(R)File 5:Biosis Previews(R)

0015839494 BIOSIS NO.: 200600184889
Hematologic improvement (HI) by TLK199 (Telintra (TM)), a novel glutathione analog, in myelodysplastic syndrome: Phase 2 study results.
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ABSTRACT: introduction: Glutathione S-transferase (GST) P1-1 has shown to be an important negative regulator of cellular growth and differentiation. The effect is mediated through binding to Jun kinase (JNK) which causes a decrease in kinase activity. TLK199, a novel analog of glutathione, binds selectively to GSTP1-1 resulting in its dissociation from JNK and subsequent kinase activation. Exposure of hematopoietic progenitor cells to TLK199 led to activation of JNK followed by cellular growth and maturation. TLK199 has shown significant myelostimulant activity in vitro in human bone marrow cell cultures as well as in several in vivo preclinical models of myelopoeisis. In Phase 1, TLK199 treatment resulted in hematologic improvement (HI) in MDS patients at all dose levels. Methods: The objectives of this multicenter Phase 2 study in MDS were to determine the safety (by NCI-CTC) and efficacy (by modified IWG MDS response criteria) of two dose schedules of TLK199 HCl Liposomes for Injection administered at 600 mg/m(2) over 60 minutes by constant rate IV infusion daily x 3 or daily x 5 every 3 weeks. Patients (pts) were treated until lack of response or unacceptable toxicity. Results: 52 MDS pis (33 M/19 F),(29 RA, 9 RARS, 8 RAEB, 3 RAEB-t, 1 CMML, 2 UK), median age 69 years (range 22-90), received 244+ cycles (1099+ treatments), median 4 (range 1-13+). Thirty-seven pis (71%) were red cell transfusion dependent and 10 pts (19%) were platelet transfusion dependent prior to entry. Pts had failed a median of 1 prior therapy (range 0-6) including: erythropoietin (27/52%), G-CSF (9/%17%%), thalidomide (10/19%), azacitidine (7/14%), steroids (6/12%), hormones (2/4%), and other therapies (14/27%). Thirty-nine pis were evaluable for efficacy. 32 pts (82%) experienced HI in one or more blood cell lineages, 14 of 16 pts (88%) with trilineage dysfunction, 8 of 13 pts (62%) with bilineage dysfunction, and all 10 pis (100%) with unilmeage dysfunction experienced HI Lineage response was HI-P (14 of 22/64%), HI-N (9 of 27/33%), and HI-E (22 of35/63%). Responses were accompanied by clinical symptom improvement, decreases in RBC and platelet transfusion requirements including transfusion independence and improvements in bone marrow maturation, differentiation, M/E ratios, and dysplastic morphology. Most common adverse events were mild to moderate acute infusion related reactions commonly seen with liposomal formulations: back pain (9/%17%%) nausea (8/15%), chills (8/15%), and bone pain (6/12%). Conclusions: TLK199 is well tolerated and an active agent in all FAB types of MDS. These data support the further clinical development of TLK199 in MDS as well as in other hematologic malignancies characterized by cytopenias.

1/7/11
DIALOG(R)File 5:Biosis Previews(R)

0015838949 BIOSIS NO.: 200600184344
Comparison of CXCR-4 and adhesion molecule expression in healthy bone marrow with expression in bone marrow and peripheral blood of patients receiving G-CSF plus AMD3100.
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ABSTRACT: It is known that the crosstalk between adhesion molecules, bone marrow microenvironment, and cytokines facilitates the multi step process of stein cell mobilization from bone marrow to peripheral blood. A combination of G-CSF plus AMD3100 - a CXCR- antagonist - has been shown to be safe and efficient in stem cell mobilization of healthy donors and cancer patients. Nevertheless, data predicting the efficacy of this approach are still missing. The present study investigated the correlation of the expression of CXCR-4 (CD184) and adhesion molecules with the kinetics and efficacy of stem cell mobilization in nine patients with Multiple Myeloma (MM) or NHL, respectively. Steady-state mobilization was performed using a combination of G-CSF (Filgrastim, 10 mu g/kg/d, 8 am) for 4 days followed by AMD3100 (240 mu g/kg) on day 4 at 10pm. Autologous aphereses were started on day5. Bone marrow and peripheral blood (PB) before AMD3100 application (day4) and PB on day 5 were investigated with a 4-color flow cytometric procedure. Bone marrow aspirates of healthy donors m=20) served as control. The qualitative (%) and quantitative (mean fluorescence intensity, [MFI]) antigen expression of CXCR-4 in relation to CD34 was assessed as well as the expression of certain adhesion molecules including LEA-1, PECAM-1, VLA-1, L-selectin and CD44. First, the median percentage of CXCR-4 surface expression in healthy bone marrow was significantly higher (92%; range: 52 - 99%) than in patients bone marrow (70%; 30 - 88%; p = 0.002), PB before AMD3100 (87%; 35 - 97%; p=0.050) and on day 5 (%17%%; 2 - 74%; p < 0.001), whereas cytoplasmic expression was comparable (91 %; 53 - 95%) in all cell compartments. The median quantitative CXCR-4 surface expression was significantly decreased in PB on day 5 compared to pre AMD3100 (14 vs. 95; p=0.003). Furthermore, the qualitative expression of LFA-1 and the quantitative expression of LFA-1, PECAM-1, VLA-1, and CD44 were also downregulated in response to AMD3100 (p < 0.010). Second, a median of 63/mu l (range: 15 - 132/mu l) CD34+ cells was measured in the PB on day 5. Thus, a high absolute count of CD34+ cells in the PB on day 5 significantly correlated with lower qualitative and quantitative CXCR-4 expression in the same material (r = 0.833; p = 0.015). Evaluating CXCR-4 expression in bone marrow, PB before AMD3100 and on day 5 no significant correlation to CD34+ counts could be detected. However, there was one very poor mobilizing patient (15/mu l CD34+ cells on day 5) in whom the quantitative CXCR-4 expression in the bone marrow was significantly higher than the median of all patients (MFI 95 vs. 26). Furthermore, some of the adhesion molecules (L-selectin, VLA-4, and CD44) showed a rather positive correlation with CD34 count. In summary, these preliminary data suggest that the amount of CD34+ cells in the peripheral blood after

G-CSF plus AMD3 100 application seems to be negatively correlated with CXCR-4 expression. A higher quantitative CXCR-4 expression in the bone marrow pre AMD3100 might predict a lower mobilization efficacy.

1/7/12
DIALOG(R)File 5:Biosis Previews(R)

0015838939 BIOSIS NO.: 200600184334
A prospective study of G-CSF primed bone marrow from pediatric donors as a stem cell source for allogeneic bone marrow transplant: A pediatric blood and marrow transplant consortium (PBMTC) study
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ABSTRACT: Higher bone marrow cell dose has been associated with improved survival after allogeneic BMT. Although PBSC provides higher cell dose, it also provides a higher number of T cells which increases the risk of GVHD and may negatively impact the outcome in pediatric patients. A prospective multi-center trial was conducted to evaluate the safety and feasibility of G-CSF primed bone marrow in children receiving HLA-identical sibling bone marrow transplantation (BMT). Thirty eight children at 9 different centers. %17% female and 21 male with a median age of 9.8 years (range 0.8-%17%) were enrolled between May 2003 and May 2005. Fifteen patients had high risk diseases (ALL >= CR2=4, AML >= CR2/refractory=5, Advanced MDS=3, JMML=1, NHL=2) and 23 had standard risk disease (SAA=6, Red Cell Aplasia=, Sickle cell disease=1, CML-CP=2, AML CR1=9, ALL CR1=2, MDS-RA=2). Five patients had undergone a prior allogeneic transplant. All patients received myeloablative preparative regimens (Cy/TBI +/- VP-16=12, BU/Cy other=20 and Cy/ATG=6) and 32 (84%) received CSP/FK506 with MTX as GVHD prophylaxis. Donors were HLA identical siblings except for one who was syngeneic. Donors with median age of 9.2 y (range 1.1-22) received 5 mcg/kg/day of GCSFSQ for 5 consecutive days. Bone marrow was collected on the fifth day with a median volume of 14.5 cc/kg (range 5.2-25). No donor experienced any complications related to G-CSF administration or harvest, up to the time of last follow-up at one month after the harvest. The absolute CD34 cell count at the day of the harvest was measured in %28% patients and it was significantly higher in bone marrow compared to peripheral blood, median of 50/mu l (8-247) vs 513/mu l (116-156) respectively ($p < 0.0001$). Median nucleated and CD 34 cells infused was 8.4x10(8)/kg (range 2.4-60.9) and 8.7x10(6)/kg (range 2-27.6) respectively. No G-CSF was administered post transplant. All patients had neutrophil engraftment at a median of 19 days (13-%28%), and all but one patient with early post-transplant relapse had platelet engraftment at a median of 20 days (9-44). Thirteen patients (35%) developed grade 2 GVHD and 4 of 34 evaluable patients (12%) developed chronic GVHD Q limited and 1 extensive). There was no transplant related mortality. Among 30 patients with malignant disorders 9 (30%) relapsed (6 with high risk and 3 with standard risk disease). The EFS and OS of patients with standard disease at 1 year is 84% (95% CI 68-100%) and 95% (95% CI 87-100) respectively. With a median follow up of 1 year the estimated EFS and OS of all patients at one year is 76% (CI 62-93) and 92% (95% CI 83-100) respectively. We conclude that G-CSF primed bone marrow from pediatric donors is safe and can result in high NC and CD34 cell dose that facilitate engraftment after myeloablative BMT without a discernable increase in the risk of GVHD. A prospective randomized trial comparing G-CSF primed bone marrow to unstimulated marrow is planned.

1/7/13
DIALOG(R)File 5:Biosis Previews(R)

0015838936 BIOSIS NO.: 200600184331
The CXCR4-antagonist AMD3100 augments the number of mobilized peripheral blood progenitor cells (PBPC) when added to a G-CSF standard mobilization regime and AMD3100-mobilized PBPC result in rapid hematopoietic reconstitution after autologous transplantation
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ABSTRACT: Sufficient mobilization of peripheral blood progenitor cells (PBPC) is pivotal for successful autologous transplantation. G-CSF has gained a confirmed and dominant role in standard mobilization regimens. Recent reports provided evidence for the importance of the SDF1/CXCR4 axis in hematopoietic stem cell trafficking. AMD3100 is a CXCR4 antagonist that induces rapid mobilization of CD34+ cells in healthy volunteers. We initiated a phase II study assessing the safety and potential of AMD3 100 in patients with multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). At the time of the report 6 patients with MM and 4 patients with NHL were enrolled (5 female, 5 male; age median 44, range 44-71 yrs; prior chemotherapy regimens median 3, range 1-8). All patients with MM were in stage IIA or IIIA. Patients with NHL were in stage 1113, IIIA, IIIE or IV. Mobilization treatment consisted of 5 days G-CSF (10 mu g/kg, s.c. AM) and a single dose of AMD3100 (240 mu g/kg, s.c.) in the evening of day 4, 10-11 hours prior to leukapheresis. As expected, following 4 days of G-CSF treatment the CD34+ cell count in the peripheral blood increased 22-fold (range 7,833) and there was a correlation between baseline and day 4 PB CD34+ counts (r=0,88). Addition of AMD3100 led almost to a tripling of circulating CD34+ cells within 10 lt after administration (2,8-fold increase, range 1,85-4,74). On the other hand, there was no mobilization of B-cells (CD 19)-thus giving no indication for the co-mobilization of tumor cells- and no mobilization of NK/T-cell subsets (CD2, CD3, CD4, CD8). Patients with low starting PB CD34+ counts profited most. There was no association between the SDF11-3A polymorphism and the mobilization efficiency following AMD3100+G-CSF vs. G-CSF mobilization: 21% of patients showed the heterozygous G/A phenotype and the remainder the G/G phenotype. Interestingly, SDF1-serum levels in patients increased significantly after addition of AMD3100. Per leukapheresis procedure 4,3 (range 2,6-12,1) *10e6 CD34+ cells/kg body weight (bw) were collected. Adverse effects were mild, one patient reported of nausea and emesis, WHO grade I. To date, four patients have been transplanted after high-dose chemotherapy (Melphalan 200mg/m2 or BEAM) with 4,7 (range 2,4-6,05) * 10e6 CD34+ cells /kg bw. Hematopoietic reconstitution (leukocytes > 1/nl and thrombocytes > 20/nl) was observed within a median of 14 (range 12-%17%) and 13 (range 10-15) days, respectively and is sustained in all patients. Thus CD34+ cells mobilized with AMD3100 appear to be fully functional. In conclusion AMD3 100 is a seminal new drug development in the field of stem cell transplantation with the highest potential in poorly mobilizing patients.

1/7/14
DIALOG(R)File 5:Biosis Previews(R)

0015838481 BIOSIS NO.: 200600183876
Treatment of high risk diffuse large B-cell lymphomas (DLBCL) with Ntensive induction chemotherapy, rituximab and autologous stem cell transplant.
AUTHOR: Pytlik Robert (Reprint); Trneny Marek; Belada David; Pirnos Jan; Kubackova Katerina; Jankovska Milada; Vasova Ingrid; Kozak Tomas; Pukyova Jana; Pribylova Jana; Siffnerova Hana; Zak Pavel; Hamouzova Michaela; Klener Pavel
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ABSTRACT: Background. Aggressive lymphomas with high-intermediate to high risk according to IPI or age-adjusted IPI (aaIPI) have approximately 50% probability of disease progression in two years. Previous studies of CLSG have shown that intensive induction chemotherapy combined with high-dose chemotherapy and autologous stem cell transplant (ASCT) might be benefitial in these patients (Trneny, Blood 98(11) 682a, 2001). In current study, we have explored the efficacy and tolerability of this regimen in combination with antiCD20 antibody rituximab (R) for DLBCL with 2 or 3 risk factors according to aaIPI.Methods. DLBCL patients of age 18-65 years and aaIPI 2 or 3 were eligible for the study. Treatment protocol consisted of three cycles of high-dose CHOP (MegaCHOP, cytoxan 3 g/m(2), doxorubicin 75 mg/m(2), vincristin 2 mg, and prednison 300 mg/m(2) every 21 days with G-CSF support), followed by three cycles of ESHAP and BEAM with ASCT. Peripheral progenitor cells were collected after first cycle of ESHAP. Four to six doses of R 375 mg/m(2) were given on day 1 of induction chemotherapy. As four treatment-related deaths occured in first twenty patients, prephase consisting of AOP (MegaCHOP without cytoxan) was incorporated into the treatment regimen from mid-2003. Results were analysed with intend to treat approach. Kaplan-Meier curves were constructed for survival analyses.Results. 57 patients were treated from 2002-2004. Median age was 42 years (range, 2 1 64), and 34 patients were males (60%). 39 patients (67%) had aaIPI 2 and 18 patients (33%) had aaIPI 3. %17% patients had mediastinal variant of DLBCL (30%), and 40 patients (70%) had DLBCL-other. Of 54 evaluable patients, 47 achieved CR or CRu (87%), 5 achieved PR (9%) and two progressed less than three months after treatment completion (4%). Six patients died due to treatment related toxicity (11%), four of them treated without prephase. Three other patients have life-threathening complications (6%). Only one patient (2%) progressed more than one year after study entry. Both 2-year actuarial overall survival (OS) and 2-year event-free survival (EFS) are 79% after median follow-up of 13 months and are not different for aaIPI 2 or 3 patients.Conclusion. Intensive induction chemotherapy combined with rituximab and ASCT is an effective strategy for treatment of young and high risk patients with CD20 positive

1/7/15
DIALOG(R)File 5:Biosis Previews(R)

0015837904 BIOSIS NO.: 200600183299
Primary mediastinal large B-cell lymphoma (PMBL) outcome is significantly improved by the addition of rituximab to dose adjusted (DA)-EPOCH and overcomes the need for radiation
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ABSTRACT: Gene expression profiling has revealed that over one third of genes more highly expressed in PMBL than other DLBCLs are characteristically expressed in classical Hodgkin Lymphoma (HL) suggesting a biological relationship (J Exp Med 198:851, 2003). PMBL and HL also share mediastinal presentation, young age, female predominance, prominent sclerosis and CD30 expression. Although some cases lie in a pathological "grey zone" between HL and PMBL, the latter is distinguished by robust CD20 expression. Like HL, local mediastinal failure after doxorubicin-based regimens has led to routine mediastinal xRT, which is associated with secondary malignancies and coronary disease. We analyzed the outcome of DA-EPOCH in 36 untreated PMBLs. No fits received xRT except for CNS PMBL. DA-EPOCH was administered with G-CSF for 2 cycles beyond CR for 6 to 8 cycles as described (Blood 99:2685, 2002). The first 14 pis were on a DA-EPOCH study and the last 22 on a DA-EPOCH-Rituximab study. Most fits had adverse prognostic features with bulky disease, elevated LDH and extranodal sites, which were balanced among the 2 series. IHC in 34 cases was consistent with gene expression profiling of PMBL with frequent CD20+ 33/33 (100%), infrequent CD 10+ 1/26 (4%) and variable BCL-6+ %17%/24 (71%) and MUM-1+ 8/22 (36%) expression. Tumor proliferation by MIB-1 was high with a median (range) of 82% (54-98). IHC markers were similar among the 2 series. EFS and OS are shown below with a median follow-up of 8.6 and 3.4 yrs, respectively, for fits receiving DA-EPOCH -/+ R. Rituximab was associated with a significantly improved EFS (p=0.036) and trend in improved OS (p=0.10) by 2-tailed exact log-rank test. In conclusion, pt characteristics were consistent with the clinical-pathological and molecular definition of PMBL and prognostic features were similar to other series (Haematologica 87:1258, 2002). These results suggest for the first time that rituximab significantly improves the outcome of PMBL and that DAEPOCH-R obviates routine mediastinal xRT. DA-EPOCH-R may be more effective than CHOP-based treatment because it overcomes high tumor proliferation and employs pharmacodynamic dosing. Although needing confirmation, our results suggest DAEPOCH-R without xRT is highly effective for PMBL.[GRAPHICS]que biological features. Novel therapeutic regimens, with decreased toxicity, targeting the older majority fits with BL are required.

1/7/16
DIALOG(R)File 5:Biosis Previews(R)

0015837768 BIOSIS NO.: 200600183163
Autologous stem cell transplantation after FLAG-IDA chemotherapy for high-risk myelodysplastic syndromes (MDS) and acute myeloid leukemias secondary to MDS (sAML) does not improve outcome: A PETHEMA experience in 103 patients.
AUTHOR: Sanz Guillermo F (Reprint); Mena-Duran Armando V; Ribera Jose M; Bernal Teresa; Palomera Luis; del Canizo Maria C; Tormo Mar; Sayas Maria J; Garcia-Boyero Raimundo; de la Serna Javier; Perez-Encinas Manuel; Perez-Sanchez Montserrat; Arilla Maria J; Moneva Juan J; Amigo Maria L; Benlloch Luis; Batlle Montserrat; Rayon Consuelo
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LANGUAGE: English
ABSTRACT: Background. AML conventional chemotherapy followed or not by autologous stem cell transplantation could be curative for high risk MDS

and sAML. Aim. To evaluate outcome in 103 patients enrolled in PETHEMA's FLAG-IDA protocol achieving complete remission (CR) followed by intensive chemotherapy and autologous transplantation compared to those with no further treatment. Patients and methods. 103 patients were recruited from 15 institutions starting December 1997 till December 2004. Eligibility criteria: de novo MDS with Spanish score > 2 and/or International Prognostic Scoring System (IPSS) > 1; or sAML. Induction chemotherapy was the FLAG-IDA regime (Fludarabine, cytarabine (ARA-C), idarubicin (IDA) and GCSF). Patients achieving complete remission (CR) had consolidation chemotherapy with IDA+ARAC+G-CSF. Patients younger than 65 yrs old who mobilized enough hematopoietic progenitors proceeded to autologous stem cell transplantation. Poor mobilizers were treated further either with allogeneic transplantation, if an appropriate donor was available, or with carboplatin (CBDCA) intensification. For patients older than 65 yrs CBDCA intensification was the only therapeutic option. Results. Patients had a median age of 62 yr (range, %17%-79) with a M:F ratio of 2.4:1. According to FAB classification, 2 patients had refractory anemia (RA), 1 had refractory anemia with ringed sideroblastos (RARS), 37 had refractory anemia with excess of blasts (RAEB), 23 had RAEB in transformation (RAEB-t) and 40 (39%) had sAML. Unfavorable cytogenetics according to the IPSS was found in 46 patients (45%). According to IPSS (if suitable), 9 patients were Intermediate-1, 21 Intermediate-2 and 23 were high-risk. According to the Spanish score, 3 patients had low-risk, 29 had intermediate-risk and 31 had high-risk. Sixty-six patients (64%) achieved CR and 37 patients (46%) failed (13 patients achieved partial remission; 12 had refractory disease and 12 patients died in aplasia). No variable correlated with the achievement of CR. With a median follow-up of 16 months (range, 1-80), 31 patients remained alive in continuous CR. The median event-free survival (EFS) was 11 months (range, 2-59) and the projected 3-year EFS was 29% (95% CI, 14-44). Multivariate analysis for EFS revealed poor-risk cytogenetics according to IPSS (P=0.005) as the only independent prognostic factor associated with relapse or death. Actuarial median and 3-year EFS for the 23 patients who proceeded to autologous transplantation were 10 months and 34%, not clearly different to the 10 months and 22% observed for the 35 patients treated with chemotherapy alone (P=0.67). Conclusions. CR rate after FLAG-IDA induction chemotherapy for patients with MDS is as high as that achieved with standard chemotherapy regimes in elderly patients with AML, but treatment-related toxicity remains a serious threat. Autologous stem cell transplantation did not provide any advantage in terms of EFS in comparison with chemotherapy alone in high risk MDS or sAML. These results in a homogeneous population of patients with MDS strongly disagree with those previously reported by the EBMT group.

1/7/17
DIALOG(R)File 5:Biosis Previews(R)

0015837767 BIOSIS NO.: 200600183162
Efficacy of nonmyeloablative hematopoietic cell transplant (HCT) in secondary myelodysplastic syndrome (MDS) and its impact on the primary disease.
AUTHOR: Kerbauy F (Reprint); Maris M; Storer B; Maloney D; Niederwieser D; Agura E; Pulsipher M; Chauncey T; Maziarz R; Forman S; Langston A; Wade J ; Scott B; Deeg J; Storb R; Sandmaier B M
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ABSTRACT: Allogeneic HCT is currently the only treatment option with curative potential for secondary MDS. The efficacy of nonmyeloablative HCT in patients (Tits) with secondary MDS and its impact on the primary disease is unknown. We analyzed data from 25 patients, 38-74 (median 58) years of age, with secondary MDS who were not candidates for myeloablative HCT. The primary diseases included non-Hodgkin's lymphoma (NHL) (n=11), chronic lymphocytic leukemia (CLL) (n=5), multiple myeloma (n=2), breast cancer (n=2), acute myelogenous leukemia (n=1), Hodgkin lymphoma (n=1), and other carcinomas (n=3). At the time of HCT, 19 Tits (76%), including all with non-hematologic primary malignancies, were in complete remission of the primary underlying malignancy, while 4 patients with CLL and 2 patients with follicular NHL had active disease. Twenty-four patients had received 1-6 (median 2) treatments for the primary disease 0.8-10.8 (median 6.2) years before developing MDS, including autologous HCT in 12 (48%). One patient developed MDS after local treatment for squamous cell carcinoma. The secondary MDS status at HCT was RA(RS) (n=10), RAEB/RAEB-t (n=6) or AML (n=9). The interval from MDS diagnosis to HCT was 0.2-1.5 (median 0.5) years. All Tits were conditioned with fludarabine, 90mg/m(2) and 2 Gy TBI and received unmodified G-CSF mobilized peripheral blood progenitor cells containing a median 6.2 x 10(6) CD34+ and 2.2 x 10(8) CD3+ cells/kg from HLA-matched related (n=13) or unrelated (n=12) donors. Postgrafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. All Tits had initial donor engraftment at day %28% after HCT, but 2 Tits experienced subsequent graft rejections followed by MDS relapse. The incidences of grades II, III and IV acute GVHD were %28%%, 12% and 4%, respectively. Fourteen Tits (54%) achieved complete remissions of their MDS. Fourteen (56%) patients died; 3 from non-relapse causes and 11 from relapse/progression of MDS. The 1 year estimates of non-relapse mortality, overall and progression free survivals were %17%%, 56% and 36%, respectively. The 3-year overall survival was 35% for pts with RA(RS) (n=10) and 29% for patients with more advanced disease. All Tits in complete remission of the primary disease at the time of HCT remained in remission of the primary disease after the HCT. Among four pts with active CLL at the time of HCT, one achieved CR after HCT but died from MDS progression, whereas the other 3 had stable disease at the last follow-up. Among 2 Tits with active follicular NHL, one achieved CR after HCT but died from progression of MDS and the other pt died on day 7 from multi-organ failure. In summary, nonmyeloablative HCT allowed for development of graft versus tumor effects for MDS. Encouragingly. none of the patients had relapse or progression of their primary malignancy following nonmyeloablative conditioning and post-grafting immunossupression. Additionally, HCT may control the primary disease (CLL and indolent NHL) if active at the time of HCT.

1/7/18
DIALOG(R)File 5:Biosis Previews(R)

0015837749 BIOSIS NO.: 200600183144
Treatment with rituximab, CHOP and highly active antiretroviral therapy (HAART) in AIDS-related diffuse large B-cell lymphomas (DLBCL). Study of 60 patients.
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ABSTRACT: Background and objective. Rituximab and CHOP (R-CHOP) is the most employed treatment for DLBCL, but Ins with AIDS-related lymphomas are

usually excluded from clinical trials. The objective of this open, prospective multicenter trial is to evaluate the feasibility, efficacy and toxicity R-CHOP and HAART in AIDS-related DLBCL. Patients and methods. Between April 2001 and July 2005, 60 consecutive HIV-infected Ins with newly diagnosed DLBCL were included in 20 Spanish hospitals. HAART was given to all patients from diagnosis if they were not already receiving it. Six cycles of R-CHOP were administered, IT CNS prophylaxis (MTX, ARA-C and hydrocortisone) was given in every cycle to all patients. G-CSF support was recommended Response to chemotherapy, toxicity, OS and DFS for complete responders were recorded. Results. Median age 42 yr (range 2664), 49 (82%) males, 30 (50%) with previous known diagnosis of HIV infection (median from dx HIV to NHL 10 yr, range 0.5-19). Median CD4 lymphocyte count 152/mL (range 0-905), median HIV load 19x10(3) copies/mL (range 0-2x10(6)). 36 Ins were receiving HAART at the time of NHL dx (median 3.5 yr, range 0.5-9). Extranodal involvement 43 (72%), stage III-IV 38 (63%) and 36/56 had intermediate-high or high age-adjusted IPI score. 10 patients are under treatment, 1 (2%) withdrawal, 6 (12%) induction death (infection 3, hepatic failure 2, multiorgan failure 1), 10 (20%) resistant, CR 33 (66%). After a median follow-up of 2 yr, 2-yr survival probability was 63% (95%CI 50-76). The probability of remaining alive and in first CR at 2 yr for complete responders was 89% (95%CI 77-100). Three patients died in first CR (opportunistic infection, sudden death and violent death) and no relapses have occurred to date. Virologic and immunologic responses to HAART at 6 months after the completion of treatment were maintained or achieved in %17%/21 (81%) and 14/22 (64%) of patients, respectively. Out of 245 R-CHOP cycles analysed the most frequent grade II-IV toxicities were infections (30, 12%), gastrointestinal (21.9%) and neurologic (5.2%). Conclusion. In patients with AIDS-related DLBCL the combination of HAART and R-CHOP is feasible and effective. In this trial the response rate and survival are comparable to those obtained in immunocompetent patients treated with R-CHOP.

1/7/19
DIALOG(R)File 5:Biosis Previews(R)

0015837535 BIOSIS NO.: 200600182930
High levels of early donor chimerism and treatment-responsive disease predict improved progression-free survival following non-myeloablative transplantation for advanced CLL.
AUTHOR: Brown Jennifer R (Reprint); Li Shuli; Kim Haesook; Fisher David C; Cutler Corey; Ho Vincent; Lee Stephanie J; Ritz Jerome; Antin Joseph H; J. Soiffer Robert; Gribben John G; Alyea Edwin P
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ABSTRACT: CLL remains an incurable disease with standard chemotherapy. Although recent data suggest that CLL can respond to graft vs leukemia effects, myeloablative allogeneic stem cell transplantation is associated with a high transplant-related mortality in this population of older, heavily pretreated patients. We report the outcomes of 50 patients with advanced CLL who underwent NST between January 2001 and August 2004. All patients received fludarabine 30 mg/m(2) x 4 days and intravenous busulfan 0.8 mg/kg/d x 4 days. 94% received G-CSF mobilized peripheral blood stem cells while 6% received bone marrow. Graft vs host disease (GVHD) prophylaxis included tacrolimus plus low dose methotrexate (56%) or cyclosporine plus prednisone (30%) based regimens. Most patients had a HLA-matched unrelated donor (62%), 30% a HLA-matched related donor, and 8% a HLA-mismatched donor. The median age of the patients was 53 years (range 35-67), with a median time from diagnosis to NST of 6.4 years (range 0.2-14.7). The patients were heavily pretreated, with a median of 5 prior therapies; 98% of patients had received fludarabine, 96% alkylating agents, 80% rituximab, and 32% alemtuzumab. 22% of patients had relapsed after prior autologous stem cell transplant. Most patients had active disease at time of NST, with only 16% in complete remission and 26% in partial remission. 52% of patients were in active relapse and 6% had failed to respond to any attempted therapy (induction failures). 50% of patients developed grade 4 neutropenia and their median time to neutrophil engraftment was 11.5 days. The incidence of grade 2-4 acute GVHD was 36%, and of chronic extensive GVHD 33%. Eleven of 25 patients (44%) in active relapse or induction failure at time of NST achieved an objective response. The median follow-up of surviving patients is 12.4 months (range 5.6 mos-4.0 yrs), with one-and two-year PFS 38% (95% CI 24-52%) and %28%% (13- 42%). The one- and two-year OS in this highly refractory population is 59% (95% CI 44-75%) and 48% (31-65%). Patients achieving > 75% donor-derived hematopoiesis 1-2 months post-NST had a 30% risk of relapse or death from disease, as compared to 72% for those with lower donor chimerism (p = 0.007). Relapse was the principal cause of treatment failure, resulting in 10 deaths; other deaths were due to infection (n = 5), GVHD (n = 3) and respiratory failure (n = 1). In Cox proportional hazards regression analysis considering pre-transplant parameters such as age, sex mismatch, disease status (CR/PR vs relapse/induction failure), donor type, aGVHD prophylactic regimen and Rai stage, only disease status was an independent risk factor for poor OS (HR 4.7, p= 0.02). Both older age and disease status (HR 2.7, p= 0.02) were associated with poor PFS. Although treatment-responsive disease was the primary predictor of outcome, nonetheless 44% of patients with refractory disease still achieved objective responses after NST. High levels of donor chimerism 1-2 months post-NST were associated with a reduced risk of relapse or death from disease. These results suggest that NST is a reasonable treatment option for patients with advanced CLL, and that strategies to augment donor chimerism early after NST may result in improved long-term outcomes.

1/7/20
DIALOG(R)File 5:Biosis Previews(R)

0015788572 BIOSIS NO.: 200600133967
Voriconazole replacing liposomal amphotericin B as first-line therapy in suspected or proven fungal infection in acute leukemia patients: A retrospective audit of clinical and financial outcomes in a UK district hospital.
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JOURNAL: Blood 106 (11, Part 2): p478B NOV 16 2005 2005
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ABSTRACT: Background: In most centres in the United Kingdom, systemic antifungal therapy (AFT) is used as third-line therapy for fever complicating profound, prolonged neutropenia (PPN) during the treatment of acute leukemia. Voriconazole has been recommended as first-line AFT at the Kent and Canterbury Hospital (KCH) since October 2002; liposomal amphotericin B was the previous treatment of choice. The aim of the audit was to identify numbers of episodes of PPN and the numbers of suspected fungal infections in a 2-year period following the policy change. Subsequently the clinical and financial outcomes were examined. In addition, the impact on cost of AFT following centralisation of leukemia treatment from two district hospitals onto one site was examined.Methods: A retrospective audit was conducted on data from hematology inpatients undergoing remission induction or consolidation therapy for acute

leukemia at KCH between January 2003 and December 2004. The costs of voriconazole and liposomal amphotericin B treatment from 2002 to 2004, and 8 months prior and post centralisation of inpatient care (April 2004, which increased the population from 400,000 to 600,000), were examined.Results: 84 episodes of PPN were identified in 41 patients undergoing treatment for acute leukemia; mostly acute myeloid leukemia (AML). Itraconazole prophylaxis from d1 of therapy and GCSF front d+5 was used in the majority of cases. 18 cases of suspected or radiologically proven fungal infection were identified. High-resolution computed tomography of the chest was performed in 10 cases and suspicious lesions identified in three. Voriconazole was used as first-line therapy in %17% /18 cases. In 7 cases, treatment was switched to liposomal amphotericin B. Reasons for switching were rising C-reactive protein (I patient), persistent fever (2 patients), radiological progression (I patient) and side effects (3 patients). Of the 3 patients with radiological evidence of fungal infection, two had a complete resolution (1 voriconazole, 1 voriconazole/liposomal amphotericin B) and 1 patient died of refractory leukemia. There was a fall in total antifungal spend from 263K pound in 2002/3 to 229K pound in 2003 and a further 68% fall to 73K pound in 2004. We suspect this was due to increasing adherence to the new antifungal protocol and to improved practices following centralisation: in the 8 months pre-centralisation the antifungal spend across all hospitals was 102K pound falling by 74% to 26K pound in the 8 months on the single site.Conclusion: Since introducing voriconazole as first-line AFT, centralising inpatient services, and adopting common policies for antimicrobial prophylaxis, there has been considerable financial benefit with no increase in morbidity and/or mortality.

1/7/21
DIALOG(R)File 5:Biosis Previews(R)

0015788471 BIOSIS NO.: 200600133866
CD3 depleted hematopoietic peripheral blood stem cell grafts in children with refractory hematologic malignancies undergoing transplantation from mismatched related donors.
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JOURNAL: Blood 106 (11, Part 2): p451B NOV 16 2005 2005
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ABSTRACT: Allogeneic HSCT is the only curative intervention for patients with persistent disease or who recur after transplantation; however, these patients are often not considered for HSCT because of their persistent disease or high risk for regimen-related toxicity. We conducted a prospective study for patients who had hematologic malignancies with refractory disease or who relapsed after allogeneic HSCT using mismatched family member donors and a reduced intensity conditioning regimen in an effort to allow GVHD to occur to reduce disease recurrence in this high risk patient population. The conditioning regimen consisted of fludarabine (40 mg/m(2)/day for 5 days), melphalan (60 mg/m(2)/day for 2 days), and thiotepa (10 mg/kg/day for one day). One dose of melphalan was omitted in 6 patients who were aplastic at the time of transplantation. OKT3 was administered from day -9 to +%17% for prevention of graft rejection. GVHD prophylaxis consisted of MMF initiated on day -2. Rituximab 375 mg/ml(2) was administered on day 0 as EBV prophylaxis. Patients received G-CSF starting on day +6 until ANC >= 2000/min(3) for two consecutive days. Peripheral blood grafts were obtained after mobilization with G-CSF and GM-CSF. Grafts were depleted of T-lymphocytes on the CliniMACS device using the anti-CD3 antibody OKT3. 25 patients were treated in this manner: 10 with refractory disease and 15 requiring another allogeneic HSCT (14 had one prior HSCT, one had 2 prior HSCT). For refractory patients, diagnoses included AML (2 secondary AML, 1 persistent disease (PD)) JMML (n=1 PD), ALL (n=3, PD), and NHL (n=3, PD including one after autologous HSCT). For patients who had failed prior allogeneic HSCT, diagnoses included AML (n=7), ALL (n=7), and CML (n=1. blast crisis). Patients had failed HSCT from matched sibling donors (n=5), unrelated donors (n=5), unrelated cord blood grafts (n=2), and haploidentical parents (n=3). Patients were a median of 11 years old at HSCT (range, 1-26). The median number of CD34(+)cells/kg infused was 13.64 x 10(6)/kg (range, 2.23-42.46); the median number of CD3+ cells/kg infused was 0.122 x 10(6)/kg (range, 0.006-0.45). Two patients suffered primary graft rejection: one with refractory JMML recovered with persistent disease after OKT3 and a re-infusion of paternal PBSCs. The second underwent infusion of the original unrelated donor cells and engrafted. The 23 evaluable patients had a median time to ANC >= 500/mm(3) of 10 days (range, 7-12) post-HSCT. One patient undergoing second HSCT developed secondary graft rejection requiring infusion of original sibling donor marrow. 13 patients developed acute GVHD, but only 2 developed grade 3-4 acute GVHD. 5 patients developed chronic GVHD. None developed VOD. Of the refractory patients, 7 died of relapse and 1 of regimen-related toxicity. Of those undergoing subsequent HSCT, 6 died of relapse and 2 of regimen-related toxicity. With a median followup of 472 days, (range, 147-767), 9 remain alive. Transplantation of mismatched related donor PBSC grafts using OKT3 for ex vivo T-cell depletion following a reduced intensity conditioning regimen produces favorable outcomes with acceptable toxicity in this this high-risk patient population.

1/7/22
DIALOG(R)File 5:Biosis Previews(R)

0015788453 BIOSIS NO.: 200600133848
The overview of the short term curative effects of HLA haploidentical hematopoietic stem cell transplantation for hematological malignancies.
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JOURNAL: Blood 106 (11, Part 2): p446B-447B NOV 16 2005 2005
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ABSTRACT: From May 2003, 13 patients with refractory hematological malignancies received HLA haploidentical hematopoietic stem cell transplantations in out BMT center.13 patients, including 9 male and 4 female, are with an average age of 31.4 years (range, 15 to 46). Among them, 4 cases were of accelerated phase of CML, 1 blast phase of CML, 1 polyleptic ANLL-M3, 1 ANLL-M2, 2 ANLL M4, 1 ANLL M6, 2 NHL, and 1 MDS-RA. Of the 13 donors, 8 were the mothers of the recipients, 4 were the siblings, and the rest was the son. All the donors were HLA haploidentical matched to the patients.4 patients were conditioned with CY/TBI/Ara-C regimen, (Ara-C 3. 0g/m(2), q12h, x3 d; CTX45 mg/kgx2 d; TBI 5 Gy x2 d, ATG5 mg/kg x4 d)). 8 patients were conditioned with improved BU/CY regimen, (BU 4 mg/kg x3 d, CTX 1.8 g/m(2) x2 d, Ara-C 2 g/m(2) x1 d, Me-CCNU 250 mg/m(2) x1 d, ATG5 mg/kg x4 d) and 1 patient of MDS-RA was conditioned with nonmyeloablative regimen (Fludarabine30mg/m(2)/dx5d, CTX 30mg/kg/d x 2d, TBI 300 cGy d1.G-CSF was given to the donors at 250 mg/day for a continuous 5-7 days. On the 4th-8th day, their bone marrow was collected under epidural anesthesia. In the simple bone marrow transplantation, the amount of the bone marrow collected was 15 similar to 20 ml/kg recipient b.w. And BMT associated with HSCT was given to 9 of the patients. The average parameter of the mononuclear cells re-infused

was 8.84 x 10(8)/kg; while the CD34(+) cells was 2.67 x 10(6)/ kg.The treatments of CsA, MTX, MMF, ATG, and anti-CD25 monoclonal antibody were given as prophylaxis for GVHD. All the 13 patients received standard supportive care, and got hematopoietic reconstitution. The mean time of engraftment with neutrophil count more than 1.0 x 10(9)/L was 15 days and platelet count more than 20 x 10(9)/L was 21 days. All the patients was tested with STR-PCR, and showed a genotype the same as the donor's.5 of the 13 patients suffered grade I similar to II acute GVHD. 1 patient suffered grade III dermo-GVHD 30 days after transplantation. The CMV-DNA of 3 patients turned out positive after the transplantation, 2 patients suffered grade I similar to II hemorrhagic cystitis. There were totally 2 deaths, one of which who was in the IV phase of NHL died due to recurrent disease after the transplantation, the other suffered graft rejection on the %28% day of the hematopoietic reconstitution, which complicated with centrum infection after the second transplantation.11 recipients got CR after transplantation. I patient of the accelerated phase of CML relapsed on the +70 day and 1 M3 patient relapsed 18 months after transplantation, both of them died after ineffective therapy. One patient of accelerated phase of CML relapsed genetically 1 year after the transplantation, and then got remission after the administration of Glivec. Full donor-type engaftment was sustained successfully in these 8 recipients. The patients were followed up until June 2005, with a median follow-up time of 18 months (range, 12 to 25 months).Our initial results show that the conditioning regimens, either with or without radiotherapy. are able to transplant the haploidentical hematopoietic stem cell without first T lymphocytes depletion. If ATG, mycophenolate mofetil and anti-CD25 monoclonal antibody, etc. are applied. the incidence of severe aGVHD will be decreased. 8 of the 13 patients survived for more than one year after transplantation. It shows favorable short-term curative effects.

1/7/23
DIALOG(R)File 5:Biosis Previews(R)

0015788425 BIOSIS NO.: 200600133820
Successful reversion of chronic myelogenous leukemia with myelofibrosis by allogeneic peripheral blood stem cell transplantation
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ABSTRACT: Objective: To observe the effect of allogeneic peripheral blood stem cell transplantation (allo-PBSCT) on hematopoietic reconstitution of chronic myelogenous leukemia (CML) and reversion of myelofibrosis (MF). Methods: A 39 years old male patient diagnosed with CML complicated with MF and hepatitis B carrier condition (HBsAg+)underwent alloPBSCT. The donor was the patient's sibling, his 48 years old sister. Six loci on HLA-A, B, and DRB1 were completely matched with that of the recipient and HbsAb(+). Four days after the administration of G-CSF (250ug/day), PBSCs were collected from the donor for 3 consecutive days. A total volume of 168 ml was harvested. A median nucleated cell (MNC) count of 8.54 x 10(8)/kg with 5.1 x 10(6)/kg of CD34+ cells were actually administered to the recipient. The conditioning regimen was busulfan/cyclophosphamide (BU/CY). The recipient was started on intravenous infusion (IV) of cyclosporine A (CSA) on Day-1 and a plasma concentration of 150-250 ng/L was maintained. IV methourexate (MTX) 10mg/m(2) was given on Days +1, +3. +6. and +11. Oral mycophenolate mofetil (MMF) was given from Days +1 to + %28% for prophylaxis of acute graft-versus-host disease (GVHD). If the concentration of hemoglobin (Hb) decreased to less than 70 g/L and/or platelet count (BPC) less thau 10 x 10(9)/L, the recipient was transfused with Co-60 25cGy irradiated and leuko-depleted red blood cells (RBCs) and/or single-donor platelets. Started from Day +3, the recipient was given G-CSF until white blood cells (WBC) increased to at least 3.0 x 10(9) /L. EPO and Interleukin-11 were also given to stimulate the proliferation of the progenitors of erythrocytes and megakaryocytes. ne recipient also received anisodamme with a 24 hour-maintenance dose to improve the microenvironment of hematopoiesis in bone marrow. Results: DNA-STR on Day +30 indicated a complete chimerism in the recipient. Bone marrow biopsy on Day +50 showed a dramatic decrease of myelofibrosis in the ground substance and active hematopoiesis. Reticulinfibers reduced to 1+. No significant change on splenomegaly was observed but the hepatitis B antigen had turned negative and HBsAb had appeared. Conclusion: 1. In order to prevent aggravation of MF, Allo-PBSCT needs to be considered as early as possible once the diagnosis of CML complicated with MF is made. 2. Transfusion with a large quantity of donor hematopoietic stem cells is beneficial for engraftment. 3. Strict Immunoinhibition of the recipient will decrease the incidence and degree of GVHD and improve engraftment. 4. The addition of agents which improve the microenvironment of hematopoiesis will enhance engraftment. 5. Recovery of the platelet count is promising post-transplantation whereas significant changes on splenomegaly was not observed. 6. Allo-PBSCT may be a promising therapy for hepatitis B.

1/7/24
DIALOG(R)File 5:Biosis Previews(R)

0015788327 BIOSIS NO.: 200600133722
Efficacy and safety of using G-CSF on day before stem cell infusion (Day-1) in hematopoietic stem cell transplantation (HSCT) - A single institution experience from India.
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ABSTRACT: Background: It is well established that recombinant human G-CSF accelerates neutrophil recovery following hematopoietic stem cell transplantation. However, the optimal timing of G-CSF following transplantation remains unknown. We have done a Phase It non randomized open label study on effects of adding an extra dose of G-CSF (filgrastim 5 mu gm/ kg) on Day -1 of HSCT.Patients and methods: Thirty nine consecutive patients who underwent HSCT in one year period were given G-CSF on Day -1 (Day before stem cell infusion) in addition to the regular doses from Day +1 till engraftment.Results: Among the 39, males were 31 and females 8 with 15 allograft and 24 autografts. The type of harvest was PBSC in 35, BM alone in land both in 3 cases. Disease wise distribution was AML-11, MM-8, NHL-6, HL-5, CML-4, MDS-2 and Aplastic Anemia, ALL and Canasopharynx 1 each. The median MNC and CD 34 doses infused were 5.4X10(8)/ Kg and 2.26X10(6)/Kg respectively. Median days of Grade IV neutropenia was 11 (range 519) and that of ANC < 100 was 6 (range 2-19). Neutropenic fever was present for a median of 10 days (range 4-19). Neutrophil engraftment and platelet engraftment occurred at Day +11(range 8-13) and Day +21(range 11-73) respectively. Median number of packed cells and platelets (SDP) transfused were 4 and 5 respectively. Mucositis was present for a median of 9 days with Grade III in 51 % (n=20) and Grade IV in 23% (n=9) patients. TPN was used in 76% (n=30) patients for a median days of 6 days. Median number of days of antibiotics use was 10 and 57% (n=22) needed 3 lines of antibiotics. Antifungals were used in 57% (n=22) and 95% of use was empirical. Infections were documented in 42% (n= 16). Median days of hospitalization

was 22 (range 13-38).Transplant related mortality was 10% (2 Auto and 2 Allo). After a median follow up of 113 days 79.71 % (n=34) patients are alive with 71 % (n=%28%) in complete remission. One patient with Ca nasopharynx had progressive disease on evaluation and one patient with peripheral T cell lymphoma developed a secondary leukemia (myeloid) post transplant.Conclusions: Addition of G-CSF on Day -1 of HSCT is safe and provides stable engraftment and acceptable results in terms of neutropenic fever, requirement of blood products, antibiotics, TPN and duration of hospital stay. It needs to be compared in randomized trials with use of G-CSF from Day +1 onwards to prove its superiority over that schedule.

1/7/25
DIALOG(R)File 5:Biosis Previews(R)

0015788306 BIOSIS NO.: 200600133701
Usefulness of recombinant human erythropoietin during induction-consolidation chemotherapy for chronic hematological lymphoid malignancies: Improving stem cell harvest and reducing blood-product support for patients receiving autologous stem-cell transplantation
AUTHOR: Bijou Fontanet D (Reprint); Tabrizi Reza; Legay Thibaut; Melot Cyril; Bouabdallah Kritno; Pigneux Arnaud; Boiron Jean-Michel; Marit Gerald
AUTHOR ADDRESS: CHU Bordeaux, Serv Malad Sang, Pessac, Gironde, France**France
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ABSTRACT: Many discrepancies remain on how to use the combination of G-CSF and Epo inpatients (pts) with hematological malignancies. Some studies have shown efficacy of this combination in autologous stem cell transplantation (ASCT) when they are used throughout the procedure, while other have demonstrated no benefit when this combination is used after ASCT particularly for Epo. We reviewed retrospectively 30 pis (NHL= 6, HD= 2, MM= 22)who received ASCT for myeloma and lymphoma between September 2003 and May 2005. The main goal of this observation was to evaluate the impact of Epo combination (epoetin beta, alfa or darbepoetin) with G-CSF during chemotherapy administered before ASCT in order to achieve a better hemoglobin (Hb) level before the ASCT procedure. We also evaluated a possible efficacy of this combination upon hematopoietic recovery, transfusion support and stem cell harvest for this population of pts. We used G-CSF (5 mu g/kg) alone after stem cell reinfusion in our therapeutic scheme. Patients characteristics were F/M 19/11; 6 pis were in complete response and 24 in partial response of their disease. Conditioning regimen preparations were standard with Melphalan at doses between 140-200 mg/m(2) (22 pts), BEAM (7 pts), Cyclophosphamide and Total Body Irradiation (1 pt). After at least 12 weeks of treatment, median Hb level before ASCT was 11.6 g/dl (8.5-14.8) and epoetin beta was used in most patients. Median CD34 cells reinfused were 4.4 (1.2-13.7) with a median number of leukapheresis of 3 (2-9). Hematopoietic reconstitution was fast according to published data and local experience, with a median duration of neutropenia (absolute neutrophils count < 0.5 x 10(9)/l) of 7 days (5-11); the median number of days with platelets counts < 20 x 10(9)/l and 50 x 10(9)/l was 3 (0-14) and 7 (2-%17%) respectively. Median transfusion requirement was 1 red cells unit (0-6) and 2 platelets units (0-8) respectively. Median duration of hospitalization was 18 days (15-26).In conclusion, the use of combined G-CSF and Epo has probably improved clinical course of ASCT by reducing transfusion requirement, duration of hospitalization and neutropenia even when it is used before ASCT. Attempts have to be made to identify the place of Epo administration during ASCT procedure. Randomized prospective study might bring some important information about influence of this combination upon stem cell harvest particularly when it is used before the ASCT during induction and consolidation chemotherapy.

1/7/26
DIALOG(R)File 5:Biosis Previews(R)

0015788294 BIOSIS NO.: 200600133689
Intermediate dose cyclophosphamide followed by sequential GMCSF and G-CSF: An efficient and predictable PBPC mobilization regimen for autografting: A single center study of two hundred and thirty patients
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ABSTRACT: Collection of an optimal dose of peripheral blood progenitor cells (PBPC), eg, > 5 x 10(6) CD34+ cells/kg, speeds engraftment after autologous bone marrow transplantation (ABMT). PBPC mobilization using high dose cyclophosphamide (Cy), eg 3-7gm/m(2) and G-CSF typically produces a higher yield of PBPC than Cy or G-CSF alone, but WBC rebound following such regimens is often unpredictable, necessitating multiple assessments of blood WBC and CD34+ cell count, may require weekend leukapheresis (1,P), and is associated with a high risk of febrile neutropenia. To minimize these problems while producing an adequate PBPC yield, we mobilized 230 unselected patients (pts) for ABMT using moderate dose Cy (1.5g/m(2), day 1), followed by sequential administration of GM-CSF (500mcg/d, days 3-7) and G-CSF (5mcg/kg/d, day 8 until completion of LPs). This "CyGMG" regimen was based upon reports suggesting a synergy between GM-CSF and G-CSE LP was initiated on day I I irrespective of WBC or blood CD34+ cell count. Cy was administered on Friday (day 1) with LP starting on Monday (day 11 = LP day 1) and 20L LPs were performed for up to six days, thus avoiding weekend LP in most pis (median #LP = 3, range 1-6). Pt median age was 53 (range 19-78); 134 male, 96 female; diagnosis; myeloma (77), NHL (94), breast cancer (%17%), Hodgkin's disease (%28%), Testicular cancer (4), other (10). Median prior chemotherapy (CT) regimens = 2 (range 0-6). The estimated (Kaplan-Meier) cumulative probability of achieving a target collection of > 2, or 5x10(6)/CD34+ cells/kg on LP days 15 was 0.5, 0.77, 0.87, 0.91, 0.93, 0.87 and 0.25, 0.5, 0.65, 0.72, and 0.74 respectively. In addition, since 12/2003 when the collection target for pts with myeloma was increased to 10x10(6) CD34+ cells/kg, 76% of myeloma pis achieved this goal. Based on multivariate cox regression, diagnosis (myeloma vs other) and day I platelet (pit) count were significantly associated with achieving 2 or 5 x 10(6)/CD34+ cells/kg and the above factors plus the # of prior CT regimens were associated with achieving 10x10(6)/CD34+ cells/kg. However, (in contrast with a previous report) the day 1 plt count was not correlated with CD34+ cells/ kg in the subgroup of myeloma pts (r=0.07, p=0.62). For non-myeloma pts a pit count > 75,000 predicted achievement of 5x10(6) CD34+ cells/kg (2/%17% pts with < 75K pit vs 91/136 pis with > 75K fill; p <.0001 by X-2). Toxicities consisted mostly of mild bone pain and fevers, and 12 patients required hospital care during mobilization (not necessarily regimen related). Conclusion: This large series indicates that the above mobilization regimen (1) efficiently mobilizes adequate PBPC in the vast majority of an unselected population of pis for ABMT (including mycloma pis with a target dose of 1x10(6)CD34/kg), (2) obviates the need for WBC and peripheral blood CD34+ cell count monitoring before commencing LP and the need for weekend LP, and (3) is

well tolerated by pts.

1/7/27
DIALOG(R)File 5:Biosis Previews(R)

0015788275 BIOSIS NO.: 200600133670
Merit of initiating peripheral blood stem cell (PBSC) collections at low level of circulating CD34+cells
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ABSTRACT: Most patients or donors undergoing leukapheresis (LP) for autologous or allogeneic PBSC transplantation requires multiple collections to achieve a sufficient CD34+ cell dose. LP is usually initiated when peripheral blood (PB) CD34+ reached a certain level, such as 20/mu l. The aim of this retrospective analysis is to summarize our institutional experience of initiating LP at a low PB CD34+ cell level of 5/mu l and investigate the merit of the practice. All patients or donors underwent LP (using Cobe Spectra or Baxter Amicus) processing 3 times the blood volume. A total of 170 LP procedures (118 autologous and 52 allogeneic) was performed in 74 adult patients or donors (> 40 kg) between Jan 2004 and May 2005. Autologous patients were mobilized with chemotherapy and G-CSF while allogeneic donors with G-CSF alone. A " good " LP product is defined as one having >= 1 x 10(6)CD34+ cells/kg so that a minimum dose of 3 x 10(6)/kg can be achieved in 3 collections. Our result showed that each PBSC product contained 6.07 x 10(8) WBC/kg (median, range: 0.13-%17%.5) and 1.59 x 10(6) CD34+ cells/kg (0.14-24.9). Total CD34+ cells in PB SC products were correlated to PB CD34+ cell counts (r = 0.79, data not shown). As shown in Table 1, initiating LP at higher levels of PB CD34+ cell increased the proportion of good LP. Nevertheless, 76% of collections initiated at > 5 CD34+ cells/mu l achieved good LP criterion. It is possible that the level of PB CD34+ cells was still increasing in many patients or donors after initiation of LP at the low level. However, some patients / donors still achieved minimim CD34+ cell dose when second LP day (Day 2) PB CD34+ cell level was lower than that of first LP day (Day 1) (Table 2). These patients / donors would likely NOT have been collected if higher levels of PB CD34+ cells were used as guideline for start of LP. Eleven patients / donors whose Day 2 CD34+ cell count was below that of Day l achieved minimum CD34+ cell dose when LP was initiated at < 20/mu l. When LP was initiated at < 10/mu l, four individuals achieved minimum dose. All 4 were autologous patients mobilized with chemotherapy and G-CSF (3 AML and 1 NHL). In conclusion, our results showed that initiating LP at low PB CD34+ cells can be helpful to some individuals. The guideline may be especially useful in those patients that can only be mobilized marginally.

1/7/28
DIALOG(R)File 5:Biosis Previews(R)

0015788274 BIOSIS NO.: 200600133669
Comparing platelet loss in 2 common apheresis machines for collecting autologous peripheral blood stem cells (PBSC)
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JOURNAL: Blood 106 (11, Part 2): p399B NOV 16 2005 2005
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ABSTRACT: Chemotherapy together with G-CSF is commonly used to mobilize patients prior to leukapheresis (LP) of PBSC for autologous transplantation. For many patients, peripheral blood platelet counts (PLT) were below 75,000/mu l when LP was initiated. Minimizing PLT loss is an important consideration, especially for these patients. The aim of this retrospective analysis is to compare PLT loss during LP for autologous PBSC in two common apheresis machines (Baxter Amicus and Cobe Spectra). Between August 2004 and May 2005, 57 autologous PBSC products were collected from %28% adult patients (weight > 40 kg) with results (mean +/- SD) summarized in Table 1. LP were collected using automated procedures and 3 times blood volume was processed. Collection efficiencies (EFF) were calculated as total cells (CD34+ or PLT) in product divided by the circulating count prior to LP times processed volume. Statistical significance was determined by impaired Student's t-test. There were no significant differences (p > 0.1) (NS) in patient age, weight, CD34+ cell count (data not shown) and PLT count prior to LP. There were also no differences in the proportion and the total CD34+ cells in the PBSC products collected by either machines. While both devices collected CD34+ cells with similar EFF (data not shown), the Amicus PBSC products have a trend (p = 0.08 and 0.07 when all LP or only those initiated with PLT count below 75,000/mu l, respectively)towards a smaller volume (VOL) and contained significantly (p < 0.05) fewer PLT than those collected by Spectra. The PLT EFF was also significantly lower with Amicus, indicating a smaller PLT loss. The same findings were observed whether all LP or only those LP initiated with low PLT counts (< 75,000/mu l) were considered. Our results showed that lower PLT loss is achieved with Amicus during autologous PBSC collection. The machine would be more appropriate for collecting patients with low PLT counts.Table 1: PLT Loss during Autologous PBSC Collection in Amicus or SpectraN Pre LP PLT(x10(3)/mu l) LP VOL(ml) LP Total PLT (x10(10)) PLT EFF(%)[GRAPHICS]e-inhibitor ZVAD-fmk, these data suggested that upon irradiation, the photoactivation of TH9402 will trigger the formation of reactive oxygen species (ROS) and the release of proapoptotic factors from mitochondria triggering various cell death mechanisms, such as caspase-dependent apoptosis, caspase-independent apoptosis, or a mixture of apoptosis and necrosis. Finally, preliminary data showed that PDT-treated cells were able to induce in vitro the maturation of monocyte-derived dendritic cells. Based on these data, we are beginning a pilot clinical study evaluating two controlled PDT conditions inducing low and high levels of apoptosis in order to assess the efficacy and biological effect of TH9402-based ECP to treat cGVHD in humans.

1/7/29
DIALOG(R)File 5:Biosis Previews(R)

0015788176 BIOSIS NO.: 200600133571
A pilot study to explore the tolerability and efficacy of thalidomide containing regimens to reduce tumour cell load prior to HSC in multiple myeloma and the feasibility of harvesting HSC following thalidomide containing regimens.
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JOURNAL: Blood 106 (11, Part 2): p373B-374B NOV 16 2005 2005

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ABSTRACT: Aim: To explore the role of thalidomide in pre-transplant induction treatment in multiple myeloma.Patients and methods: Between Sept 2002 and March 2005, 37 patients with advanced, de-novo multiple myeloma (mean age 56 years, mean Serum. albumin 33g/L, and median b -2-microglobulin 4.0 mg/L) were entered into a multicentre, phase 2 study of pre transplant induction treatment. The regimen included TDx3 (thalidomide 400mg/d, pulse dexamethasone 32mg TDS x 5d every 3 weeks PO), followed by DT-PACEx2 (thalidomide 400mg/d, dexamethasone 40mg/d x 4 PO and cisplatin 10mg/m(2)/d, doxorubicin 10mg/m(2)/ it, cyclophosphamide 400mg/m(2)/day, etoposide 40mg/m(2)/d as 4 day infusion administered 4 weeks apart, supported with G-CSF 10m, g/Kg/d). Thromboprophylaxis was warfarin (target INR 1.5-2.0) during TD and enoxaparin 40mg/day (adjusted according to platelet count) during DT-PACE. Stem cells were harvested at recovery from the second cycle of DT-PACE in the first 27 patients, but after review of the harvest results the remaining patients were harvested after first cycle of DT-PACE with an option to re-harvest after the second if the initial harvest was insufficient.Paraprotein and BJP responses and stem cell collections were compared to a historical cohort of 58 patients treated with VAD and mobilised with cyclophosphamide 5G/m(2) and G-CSF 5m g/Kg.Results: 23/37 patients completed study treatment, 21 had successful stem cell harvests. There were 2 deaths (I sepsis, I haemorrhage) and 2 failed stem cell harvests.After TD x 3 and VAD x3 the mean levels of paraprotein (or BJP) were 21% and 34% of pre-treatment levels, respectively (p=0.02). After DT-PACE x 2 and HD cyclophosphamide the mean levels of paraprotein (or BJP) were 14% and 31% respectively (p=0.014).At the completion of TDx3 42% of patients had achieved VGPR and 50% PR, whereas after VAD x 3 there was 12% CR, %17%% VGPR and 45% PR (p=0.231). Following DT-PACEx2 there was 22% CR, 39% VGPR and 26% PR and after HD cyclophosphamide there was 9% CR, 19% VGPR and 45% PR (p=0.039).The median number of CD34+ cells/kgBW harvested was 4.7 x 10(6) after DT-PACE and 11.6 x 10(6) after HD cyclophosphamide (p=0.001). The median number of aphereses procedures required was 2 for both study patients and historical controls.58 serious adverse events included 20 episodes of infection (9 during TD and I I during DT-PACE), 3 episodes of haemorrhage, I pulmonary embolus and 2 deaths.Conclusion: 1. Thalidomide dexamethasone combination appears to be as efficacious as VAD in reducing tumour burden in de-novo multiple myeloma. 2. The addition of DT-PACE improves the pre-transplant CR and VGPR rate. 3. In most patients adequate stem cell harvest can be obtained, but yields appear to be less than after VAD/HD cyclophosphamide. 4. Thalidomide dexamethasone followed by DT-PACE is associated with tolerable but not insignificant toxicity.

1/7/30
DIALOG(R)File 5:Biosis Previews(R)

0015788056 BIOSIS NO.: 200600133451
Pentostatine is a safe and active agent in chronic lymphocytic leukemia CLL with minimal toxicity.
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JOURNAL: Blood 106 (11, Part 2): p342B NOV 16 2005 2005
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ABSTRACT: Pentostatin is a nucleoside analogue,it is a potent irreversible inhibitor of adenosine diaminase ADA. The triphosphate form of pentostatin is incorporated into DNA strand breaks. This effect is potentiated by the presence of an alkylating agent such as Cytoxan. Combination approaches will maximize the inhibition of DNA repair with less myelosuppression. A total of twenty five patients diagnosed with chronic lymphocytic leukmia treated with pentostatin combination in the last four years, nineteen patients had refractory CLL. Six patients has newely diagnosis with adverse features such as high risk cytogenetic/FISH abnormality, elevated serum Beta 2 microglobuline, elevated LDH, presence of the B symptoms, doubling time less than a year and progressive enlargment of spleen and lymph nodes. All patients had stage III-IV Rai classification. Fifteen males and ten females, eighty five percent were african american. Mean age is 52 years (range 46-70). Median follow up was eighteen months (range4-42 months). Thirteen patients recieved the combination of Pentostatin,Cytoxan and Rituxan. Rituxan or Rituximab is a chiemeric human monoclonal antibodies against CD expressing B cell lymphocytes. Pentostatin 4mg/M2, Cytoxan 300mg/M2 and Rituxan 375mg/M2 given one day one every %28% days. Three patients recieved pentostatin and cytoxan. Nine patients recieved pentostatin and rituxan. Eighty percent of the patients recieved a minimum of six cycles. Complete response CR and near complete response nCR were confirmed by peripheral blood flowcytometric study. Ten patients achieved CR,nCR and fifteen patients achieved PR. One patient had short PR response less than six months post completing therapy. Five patients had autologous bone marrow transplant post CR,nCR response. Median time to progression is not reached. Toxicity observed with pentostain combination was minimal as compaired to retrospective analysis of Fludarabin whether as a single agent or in combination with cytoxan or rituxan. Bone marrow necrosis and tumor lysis syndrome were not seen. Neutropenic fever that required hospitaliztion is less than 10% as compaired to Fludarabin 40%. Growth factor G-CSF required less with pentostin combination. However, warm auto-immune hemolytic anemia was seen more during pentostatin therapy rather than prior to initiating therapy.Conclusion: Pentostatin has less myelosuppressive effect and equal response as compaired retrospectively to Fludarabine. Head to head randomized prospective study is needed.

1/7/31
DIALOG(R)File 5:Biosis Previews(R)

0015787748 BIOSIS NO.: 200600133143
Phase II clinical study of rituximab and high-dose biweekly THP-COP (pirarubicin, cyclophosphamide, vincristine and predonisolone) with G-CSF for non-Hodgkin lymphoma: Results of a multicentric study of NMLSG (Niigata Malignant Lymphoma Study Group).
AUTHOR: Takizawa Jun (Reprint); Aoki Sadao; Takai Kazue; Kurasaki Tohri; Honma Keiichiro; Higashimura Masataka; Nagai Kourichi; Momoi Akihito; Nikkuni Koji; Aizawa Yoshufusa
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JOURNAL: Blood 106 (11, Part 2): p264B NOV 16 2005 2005
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ABSTRACT: Introduction CHOP chemotherapy has been accepted as the standard treatment for patients with non-Hodgkin lymphoma (NHL), but in some histological or clinical subtypes the results are not satisfactory. We have shown the efficacy and safety of high-dose biweekly THP-COP with G-CSF support (HDBW-TCOP(G)) for NHL. In this regimen, we choose pirarubicin in stead of doxorubicin because it was proven high efficacy

against NHL and the lower toxicity than doxorubicin. Recently, the combination of rituximab and standard CHOP has been shown to have a synergistic effect for NHL. We performed a phase II multicentric clinical study to assessed the feasibility and toxicity of the combination chemotherapy of rituximab and HDBW-TCOP(G) (HDBW-R-TCOP(G)) compared with those of HDBW-TCOP(G).Patients and methods Between August 1998 and December 2004, Forty-one Japanese patients with previously untreated NHL from whom informed consent was obtained were included in this study. Median age was 45 (range 19-63) years. There were 19 males and 22 females.According to WHO-classification diagnoses, histological subtypes included follicular lymphoma (FL) 15(37%); nodal marginal zone B-cell lymphoma (NMZBCL) 2(5%); mantle cell lymphoma (MCL) 3(7%); anaplastic large cell lymphoma (ALCL) 1(2%), diffuse large B-cell lymphoma (DLBCL) 18(44%); peripheral T-cell lymphoma (PTCL) 1(2%), angioimmunoblastic T-cell lymphoma (AILT) 1(2%). Of 41 patients, one patient was stage 1, stage 2, 11 stage 3 and 16 stage 4. International prognostic index (IPI) included L 6; LI 22; HI 7; H 6. HDBW-TCOP(G) consisted of pirarubicin 70 mg/m(2) on day 1; cyclophosphamide 1000 mg/m(2) on day 1; vincristine 1.4 mg/m(2) on day 1; predonisolone 50 mg/m(2) orally from day 1 to 5; lenograstim 2.0 mu g/kg/day from day 3. Fifteen patients who enrolled after rituximab was approved in Japan received therapy combined HDBW-TCOP(G) with rituximab 375mg/m(2) on day -2 (HDBW-R-TCOP(G)). Six cycles were administered at intervals of two weeks.Results Of the 41 patients treated, 32 (78.0%) achieved a complete remission (CR) and nine (22.0%) achieved a partial remission (PR), for an overall response rate of 100%. After median follow-up of 36 months (range 2.9-81.8), progression free survival (PFS) and overall survival (OS) were 68.2% and 97.5%, respectively. PFS was 90.9% for HDBW-R-TCOP(G), and 69.5% for HDBW-TCOP(G), but no significant differences was found among two regimen. There was no significant difference in the PFS and OS between aggressive and indolent histological subtypes. 76% of patients developed Grade 4 leukopenia (according to NCI criteria) but no patients experienced febrile neutropenia. 15% of patients developed G4 anemia and %17%% of patients G4 thrombocytopenia. Other adverse effects were minimal.Conclusion Both HDBW-TCOP(G) and HDBW-R-TCOP(G) are feasible for NHL with acceptable toxicity. The excellent result suggests they are effective for aggressive NHL patients with poor prognostic factors and advanced stage indolent NHL.

1/7/32
DIALOG(R)File 5:Biosis Previews(R)

0015787443 BIOSIS NO.: 200600132838
Granulocyte colony-stimulating factor induced differentiation syndrome mimicking acute myeloid leukemia and the unmasking of chronic myelomonocytic leukemia.
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JOURNAL: Blood 106 (11, Part 2): p185B-186B NOV 16 2005 2005
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ABSTRACT: In general, the use of granulocyte colony-stimulating factor (G-CSF) has been relatively safe with only occasional reports of inducing adult respiratory distress syndrome. The mechanism for this complication is relatively unknown. A possible mechanism include the superoxide production by G-CSF causing neutrophil leakage resulting in pulmonary epithelial damage. We are reporting a 63 year old woman with a medical history of severe psoriasis and chronic thrombocytopenia with splenomegaly who presented to the emergency room with epistaxis and excessive bruising with a platelet count of 5 x 10(9)/L. She received weekly injections of efalizumab (Raptiva) for six months for treatment of severe psoriasis and was stopped five weeks prior to presentation. Methotrexate and dexamethasone were started approximately one week prior to admission for continued refractory psoriasis. G-CSF was started at 480 mcq subcutaneous once a day on day 4 of admission for neutropenia induced by either efalizumab or methotrexate. When her white blood cell (WBC) count rose from 1.9 x 10(9)/L to 6.3 x 10(9)/L the G-CSF was stopped on hospital day 8. Her absolute monocyte count also rose from 0 to 3.78 x 10(9)/L (normal range from 0.1 x 10(9)/L to 0.9 x 10(9)/L) with a left shift in the peripheral blood. The WBC and monocyte counts continued to rise and she was transferred to our hospital for further care on hospital day 11. The WBC count peaked at 147.9 x 10(9)/L on hospital day 12, with a differential of %17%% monocytes, 16% metamyelocytes, 4% myelocytes, and 1% promyelocytes. The patient gradually became short of breath at rest, requiring 2-4 liters of oxygen and developed bibasilar crackles on exam. Bibasilar infiltrates were detected on chest radiographs at the outside hospital. Upon arrival to our hospital a CT of thorax showed diffuse bilateral ground glass attenuation. WBC count decreased to 119 x 10(9)/L on hospital day 15, with a differential of 47% monocytes, 2% metamyelocytes, 3% myelocytes, and 1% blasts. A bone marrow examination showed morphologic findings consistent with acute monocytic leukemia with monocytoid cells greater than 50%. Since the WBC count continued to decrease with improvement of her respiratory symptoms no chemotherapy was given. When the WBC reached 7.4 x 10(9)/L another bone marrow examination showed a hypercellular marrow with full maturation and no excess of blasts and no evidence of acute leukemia. A background of mature monocytes (12%) and increased reticulin fibers were noted. Chronic myelomonocytic leukemia was her final diagnosis. The laboratory and bone marrow studies while under the effects of G-CSF mimicked those of acute myeloid leukemia. The use of G-CSF in this patient appeared to have unmasked an underlying CMML from an undifferentiated myeloproliferative disorder. Her development of pulmonary infiltrates, hypoxia, leukocytosis and monocytosis after receiving G-CSF appeared to be a differentiation-like syndrome. This resolved after stopping G-CSF and without high dose steroid therapy. Physicians should be aware that G-CSF can cause a syndrome that mimics AML and should refrain from starting cytotoxic chemotherapy based on bone marrow findings under the influence of growth factors. Green MD, Koelb1 H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Annals of Oncology 2003; 14:29-35.

1/7/33
DIALOG(R)File 5:Biosis Previews(R)

0015744627 BIOSIS NO.: 200600090022
Direct cardiac injection of G-CSF mobilized bone-marrow stem-cells improves ventricular function in old myocardial infarction
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ABSTRACT: Autologous transplant of bone marrow stem cells (BMSC), although extremely useful after acute myocardial events, has not been evaluated in patients with old (> one-year-old) myocardial infarction. Our aim was to determine if CD34(+)-enriched peripheral-blood cells, obtained by apheresis, injected directly into the severely damaged myocardium of five patients with old myocardial infarction could restore depressed myocardial function. We found that %28% weeks after revascularization and peri-infarction injection of the enriched CD34(+) peripheral mononuclear

cells, ventricular hemodynamic parameters that included left ventricular ejection fraction, left ventricular diastolic volume, ventricular systolic volume and left ventricular diastolic diameter approximated normal values and there was no restenosis; two patients have been followed for > 52 weeks and their parameters are within normal values. In conclusion, intramyocardial injection of easily obtained CD34(+) enriched peripheral blood cells represent an encouraging procedure for patients with severely scarred and dysfunctional myocardium. (c) 2005 Elsevier Inc. All rights reserved.

1/7/34
DIALOG(R)File 5:Biosis Previews(R)

0015654084 BIOSIS NO.: 200510348584
Irinotecan and oxaliplatin combination, as second-line treatment, in fluoropyrimidine-pretreated advanced colorectal cancer. A phase II study by the hellenic cooperative oncology group (HeCOG)
AUTHOR: Timotheadou Eleni; Papakostas Pavlos; Tsavdaridis Dimitrios; Basdanis George; Kalofonos Haralambos; Aravantinos Gerasimos; Bafaloukos Dimitrios; Fountzilas George (Reprint)
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ABSTRACT: Background. The management of patients with fluoropyrimidine-resistant advanced colorectal cancer remains investigational. Irinotecan and oxaliplatin have proved effective in first-line treatment in combination with 5-fluorouracil.Study design: From February 1998 to September 2002, 34 patients with 5-fluorouracil-pretreated advanced colorectal cancer were enrolled in the study. Median age was 67 years (range, 3276) and median performance status was 1. Twenty-one patients had multiple liver metastases. Other sites of disease included lungs, abdomen, pelvis, lymph nodes, bones and skin. They received six %28%-day cycles. of oxaliplatin (85 mg/m(2) in a 2-h infusion on days 1 and 15) and irinotecan (80 mg/m(2) in a 30-minute infusion on days 1, 8 and 15 immediately following oxaliplatin).Results: Thirteen patients (39%) completed treatment. The most common grade III-IV toxicities were diarrhea (27%), anemia (6%), neutropenia (18%), alopecia (6%) and peripheral neuropathy (6%). Thirteen patients (39%) received G-CSF support, and there were 2 episodes of febrile neutropenia. There were no treatment-related deaths. Six patients (18%) had a partial remission and another 11 (33%), disease stabilization. There were no complete remissions. Median time to progression was 6.6 months (range, 0.8-20.1) and median survival 10.6 months (range, 0.8-52.9).Conclusions: Irinotecan and oxaliplatin combination has modest activity as second,line treatment of 5-fluorouracil-resistant advanced colorectal cancer. Further research is warranted for the development of: more effective and less toxic regimens in this setting.

1/7/35
DIALOG(R)File 5:Biosis Previews(R)

0015574659 BIOSIS NO.: 200510269159
Mobilization as a preparative regimen for hematopoietic stem cell (HSC) transplantation.
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JOURNAL: Blood 104 (11, Part 1): p336A NOV 16 2004 2004
CONFERENCE/MEETING: 46th Annual Meeting of the American-Society-of-Hematology San Diego, CA, USA December 04 -07, 2004; 20041204
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytokines release HSC from marrow and thus facilitate their collection from blood. We performed studies in parabiotic mice to determine if microenvironmental niches are vacated when HSC are mobilized. In our initial experiments, ROSA26 (CD45.2+) and Pep3b (CD45.1+) (both C57BL6) mice were joined in parabiosis for 3, 6, 8 or 12 wks. Although their circulations were shared (approximately 50% of granulocytes in the blood of each parabiont had partner phenotype in allstudies), few HSC engrafted in partner marrow. Specifically, 1.0-2.5% of marrow HSC had a partner phenotype, as determined by the transplantation of marrowcells into irradiated secondary recipients (Blood 102,1249,2003). Also, few marrow granulocytes and CFU-GM had a partner phenotype, implying that marrow functions as an intact compartment in which resident HSC give rise to progenitors then mature cells. In contrast, in the spleen, 1.5-3.6% of HSC, yet 38-55% of granulocytes and CFU-GM bad a partner phenotype. We then treated each parabiont with one cycle of hG-CSF (25 ug/kg) and hSCF (200 ug/kg) sq qd x 4d on days %17%-20 of parabiosis and examined the marrow at 6 weeks (day 42). 10.1 +/- 6.2(SD)% of HSC had partner phenotype (p=0.02). When 3 cycles of cytokines were administered beginning days %17%, 24 and 31, 13.9 +/- 9.0% of marrow HSC had partner phenotype at 6 wks of parabiosis (p=0.01). Experiments were then repeatedwith AMD3100 (a SDF-1/CXCR4 axis antagonist, gift of AnorMed, Langley, BC, CA; 5mg/kg/mouse sq on day 20; n=3 pairs (6 parabionts)) to demonstrate that HSCmobilization, and not replication, was responsible for these results. At 6 wks of parabiosis, 5.9 +/- 2.9% of marrow HSC, 5.7 +/- 2.3% of marrow CFU-GM and5.6 +/- 2.8% of marrow granulocytes had partner phenotype (p=0.02), while 7.2+/- 2.7%, 44.0 +/- 3.2% and 40.0 +/- 6.1% of splenic HSC, CFU-GM and granulocytes had partner phenotype, respectively. These data imply that HSC exited marrow, transited blood, engrafted in open niches in partner marrow, and contributed (normally) to hematopoiesis. Similar percentages of HSC also engrafted in spleen. However, splenic hematopoiesis, as at baseline, derived from CFU-GM, not HSC, engraftment. We next tested a corollary of these findings. If niches are vacated after AMD3100 administration, transplanted HSC might preferentiallyengraft. Pep3b mice were treated with AMD3100 (5 mg/g sq) and 40 x 101 donor marrow cells (from ROSA26 mice) were transplanted (via tail vein infusion) 6 hlater, 2 h later, or both 2 and 6 h later (n=3 mice per condition). Control animals received donor cells but no AMD3100. Donor cell engraftment was assayedat 3m (6 h later group) and 2m (other groups, 3 in data are pending) and was significantly higher in the experimental animals than control. Engraftment was3.0 +/- 1.6, 6.5 +/- 4.9, 6.5 +/- 3.6 (SD)%, respectively, in the AMD3100-treated mice, and 0.6 +/-.9, 0.6 +/- 0.8 and 2.0 +/- 1.9% in the concurrent control studies (all p values = 0.02). Confirmatory experiments in BalbC mice (where higher engraftment rates are anticipated in control studies (Blood 98:1246,2001)) are underway. Our data argue that the number of available niches determine the number of HSC that engraft. As importantly, mobilization with AMD3100 could provide a non-toxic preparative approach to HSC transplantation for genetic (and other nonmalignant) disorders.

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DIALOG(R)File 5:Biosis Previews(R)

0015573946 BIOSIS NO.: 200510268446
Erythropoiesis is highly stimulated in CD34(+) cells in low-risk myelodysplastic syndromes (MDS) with an improper mitochondrial function
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JOURNAL: Blood 104 (11, Part 1): p138A NOV 16 2004 2004
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ABSTRACT: The apoptosis of early erythroblasts from patients with low-risk MDS, refractory anemia (RA) and RA with ringed sideroblasts (RARS), is mediated through a constitutive cytochrome c (cyt c) release from mitochondria (Tehranchi etal, 2003). Moreover, mature erythroblasts in RARS, but not in RA, show mitochondrialaccumulation of aberrant ferritin (MtF) (Cazzola etal, 2003). This study aimed at further describing the pathophysiology of ineffective hematopoiesis in low-risk MDS, by studying cyt c release and MtF expression during erythroid differentiation and mitochondria ATP production in MDS bone marrow cells. We assessed freshly isolated CD34(+) cells and day 4-14 erythroblasts from RARS, RA and normal bone marrow (NBM). CD34(+) cells from all individuals were negative for MtF. NBM showed only few positive cells (0-4%, d4-14), and RA erythroblasts a median of 3% (0-8%) MtF(+) cells. RARS erythroblasts, on the contrary, showed an early increase in MtF(+) cells and acontinuous increase during the culture period (d4=10%, d7=%17%%, d14=19%). There was a positive correlation between MtF expression and cyt c at day 14 (r(2)=0.8). There was no significant difference in mitochondria ATP production between RARS, RA and NBM (all complexes or cyt c-dependent complex TV). Wefound a significant over-expression (mRNA) of the pro-apoptotic genes for cytc, Bid and Bax at day 0. Moreover, genes involved in erythroid differentiation were significantly up-regulated in MDS CD34(+) cells: 6-fold for GATA-1 and 23-fold for beta-globin; p<,0005 for both. GATA-1 and beta-globin expression increased during normal erythroid maturation, but in MDS erythroblastsGATA-1 declined and beta-globin showed only a weak increase. Comparing RARS with RA, the former showed both higher expression of the beta-globin and,GATA-1genes, and a higher degree of cyt c release and MtF expression. This indicates that the cellular abnormalities leading to erythroid apoptosis as well as efforts to compensate for these defects are present at the stem cell level in RARS. G-CSF that reduces cyt c release in MDS erythroblasts (RARS>RA) showed no effect at all on ATP production or cyt c mRNA. Moreover, G-CSF tended to increase MtF expression in some RARS erythroblast cultures, indicating that it allows survival of proapoptotic MDS erythroblasts rather than addressing the causeof apoptosis. In conclusion, the aberrant MtF expression of RARS erythroblasts occurs at a very early stage of erythroid differentiation and is paralleled by an up-regulation of genes involved in erythroid differentiation. Alternative mechanisms may be involved in RA pathogenesis, since these cells show cyt c release but only moderate MtF expression, and less gene up-regulation.

1/7/37
DIALOG(R)File 5:Biosis Previews(R)

0015573917 BIOSIS NO.: 200510268417
CD133(+) hematopoietic cells successfully reconstitute hematopoiesis following autologous peripheral blood stem cell transplantation.
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JOURNAL: Blood 104 (11, Part 1): p130A NOV 16 2004 2004
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CD133 is a unique antigen found on hematopoietic precursor cells, with a limited expression on non-hematopoietic cells. These features make it an attractivemarker for obtaining tumor-free hematopoietic grafts. We conducted a prospective clinical trial for patients with solid tumors and lymphomas who required autologous HSCT. I I children (6 male, 5 female) had CD133+ peripheral blood stem cells (PBSC) collected for subsequent autologous HSCT. The median age was 12.4 yrs (range, 2.2-26). Diagnosis included Hodgkin lymphoma (I stable disease, 2 PR), neuroblastoma (2 PR), NHL (2PR), Ewing sarcoma (I stable disease), CNS PNET (I PR), and desmoplastic small round cell tumor (I PR). All had received printing chemotherapy with growth factor support. PBSC were collected in I or 2 procedures when the absolute CD34+ count was >= 40/ul. A stem cell productwas cryopreserved as a backup. The PBSC product was processed on the CliniMACS device with positive selection methodology using the CD133 antigen. Prior toCD133 selection, the graft contained 0.3-4.9% CD34(+) cells and 0.3-4.4% CD133(+) cells. Following CD133 selection, the graft contained 45.1-98.4% CD34(+) cells and 45.9-98.8% CD 133(+) cells. The stem cell products contained a median of 5.4 x 10(6) CD34(+)/kg (range, 2.61-7.89) and 5.3 x 10(6) CD133(+)/kg (range, 2.54-8.04). One patient who had PBSC collected has not yet proceeded to HSCT. All were conditioned with busulfan 37.5 mg/m(2)/dose for 16 doses and melphalan 70 mg/m(2) for 2 doses. A cell dose from 2 x 101 CD 133(+)/kg to a maximum of 8 X 10(6) CD133(+)/kg was infused. G-CSF 5 mcg/kg/day was initiated on day 5 and continued until ANC >= 3,000/mm(3) for 2 consecutive days. All 10 patients engrafted and no patient required infusion of the back-up stem cell product. No infusion reactions were observed during infusion of the stem cell product. The median time to ANC >= 500/mm(3) was day + I I (range, 10-13) for all 10 patients. Of the 8 evaluable patients (I had hemorrhagic cystitis, I severe epistaxis), all achieved an unsupported platelet count of greater than 20,000/mm(3) at amedian of day + %17% (range, 12-20). This trial demonstrates that infusion of CD133+ hematopoietic cells can reconstitute hematopoiesis following myeloablative HSCT. Further studies are needed to describe the ability of CD133 selectionto obtain tumor free hematopoietic grafts.

1/7/38
DIALOG(R)File 5:Biosis Previews(R)

0015573915 BIOSIS NO.: 200510268415
Immunoglobulin G Fc polymorphism is correlated with rituximab-induced neutropenia following autologous hematopoietic cell transplantation.
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JOURNAL: Blood 104 (11, Part 1): p129A NOV 16 2004 2004
CONFERENCE/MEETING: 46th Annual Meeting of the American-Society-of-Hematology San Diego, CA, USA December 04 -07, 2004; 20041204
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Rituximab has been given following autologous hematopoietic cell transplantation (HCT) for recurrent or refractory B cell lymphoma with the goal of eradicating minimal residual disease. Our recent study showed that this is a feasible strategy although transient grade 3 or 4 neutropenia was observed in 51% of patients (Blood 103:777, 2004). We also reported that two IgG Fc receptor (Fc gamma R) polymorphisms, Fc gamma RIIIa 158 V/V and Fc gamma RIIa 131 H/H genotypes, predict response to rituximab therapy in patients with follicular lymphoma, probably due to their role in the antibody-dependent cellular cytotoxicity (ADCC) (JCO 21:3940, 2003). In the current report, we correlated Fc gamma R

polymorphisms with clinical outcomes after post-transplant rituximab. A total of 35 patients with diffuse large cell (25 patients), mantle cell (3 patients), transformed (3 patients) or other (4 patients) subtypes of B cell lymphoma received high-dose therapy, autologous HCT and rituximab, administrated as 4-weekly infusions (375 mg/m2) starting around day 42 and 6 months after HCT. GenomicDNA was available for Fc gamma R polymorphism analysis in 33 cases. For the Fc gamma RIIIa polymorphism, 4 (12%) patients were homozygous valine/valine (158 V/V), 14 (42%) patients were heterozygous valine/phenylalanine (158 V/F) and15 (46%) patients were homozygous phenylalanine/phenylalanine (158 F/F). For the Fc gamma RIIa polymorphism, 8 (24%) patients were homozygous histidine/histidine (131 H/H), 16 (49%) patients were heterozygous histidine/arginine (131 H/R) and 9 (27%) patients were homozygous arginine/arginine (131 R[R). We did not find a correlation of either the Fc gamma RIIIa V/F polymorphism or the Fcgamma RIIa H/R polymorphism with time to relapse after HCT. But the small number of relapses limited our power. Although rituximab infusions were well tolerated in this group of patients, 32% of the treatment courses in this study were associated with rituximab-induced grade 3 or grade 4 neutropenia (ANC < 1000/mu l), which was recorded in 51% of patients. These neutropenic episodes were not associated with infection and responded well to G-CSF treatment. The reason for this high incidence of rituximab-induced neutropenia is unclear. Amongthe 33 patients analyzed for Fc gamma R polymorphisms, Fc gamma RIIIa 158 V/Vhomozygotes experienced relatively greater neutropenia (V/V : 3/4, 75%; V/F: 8/14, 57%; F/F: 5/15, 33%). For the 57 treatment courses, the Fc gamma RIIIa 158 V/V genotype was associated with a greater chance of rituximab-induced neutropenia, compared to F carriers (158 V/F and 158 F/F). The incidence of rituximab-induced neutropenia was 71% for V/V, 39% for V/F, 19% for F/F and %28%% for F carriers (V/V vs F carriers, p = 0.035). In contrast, the Fc gamma RIIa H/R polymorphism had no impact on rituximab-induced neutropenia. Although the mechanism of rituximab-induced neutropenia is unknown, this report implicates an Fc gamma R-mediated process, such as ADCC. It is possible that B cell depletionby rituximab affects either directly or indirectly cytokine (e.g. G-CSF) production as a mechanism for neutropenia. It will be of great interest to study the correlation between Fc gamma R polymorphisms and the prevalence and duration of B cell depletion after rituximab therapy in larger clinical studies both after HCT and in conjunction with other myelosupressive therapies.

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DIALOG(R)File 5:Biosis Previews(R)

0015573621 BIOSIS NO.: 200510268121
In vitro purging in autologous stem cell transplantation for chronic lymphocytic leukaemia. A retrospective analysis on behalf of the chronic leukaemia working party of the EBMT.
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JOURNAL: Blood 104 (11, Part 1): p45A-46A NOV 16 2004 2004
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: High dose therapy (HDT) and autologous stem cell transplantation (ASCT) is part of the therapeutic strategy in a subset of patients with chronic lymphocyticleukaemia (CLL). There are no data evaluating in Vitro purging in CLL.We started a retrospective study comparing CLL receiving HDT and ASCT with either unpurged or purged autograft. Adult patients > 16 year old (y.o), with B CLL, autografted with peripheral blood, from 1992 to 2002 were selected. Enoughdata in the EBMT registry were available for 210 patients. Autograft was unpurged in 130 patients, and purged in 80 patients. Purging consisted of CD34 positive selection in 62 patients, CD34 positive and CD19 negative selection in 11 patients, a negative selection alone in 4 patients, the technique was unknown in 3 patients.Comparison of distribution for unpurged versus purged ASCT showed a sex ratio male/female of 5.1 and 2.5 (p=0.03) respectively, a median age of 52 yo and 50yo (p=0.57) respectively, a Binet stage at diagnosis of 27% and 30% for stageA, 44% and 50% for stage B, 29% and 20% for stage C (p=0.55) respectively. The majority of patients received a combination of G-CSF and chemotherapy for stem cell mobilisation (86% and 84% respectively), the median time from diagnosis to mobilisation was longer for unpurged (30 months) than for purged ASCT (18months) (p=0.016). Comparison of characteristics at transplants showed no difference for the status at transplant: 33% of patients with unpurged ASCT were in complete remission (CR) and 33% with purged ASCT; 61% and 57% were in partial remission (PR) respectively, 6% and 10% were in stable/progressive disease respectively (p=0.56). HDT comprised total body irradiation for 30% of unpurged and 72.5% for purged ASCT (p < 0.0001). The median dose of CD34 positive cells infused was 3.2x106/kg and 2.6x106/kg respectively. The majority of patients engrafted: 98.5% and 96.3% respectively. There was no difference for neutrophil recovery (l l days and 12 days respectively) and platelet recovery (%17% days and 20 days respectively).Comparison of outcome at 3 years for unpurged and purged ASCT showed aleukaemia free survival (LFS) of 40% and 55% (p=0.10) respectively, a relapse incidence (RI) of 52% and 37% (p=0.07) respectively, a non relapse mortality (NRM) of 8% and 8% respectively. According to the status at transplant LFS was identical for patients in CR: 55% and 57% for unpurged and purged respectively. For patients in PR, LFS was 25% and 58% (p=0.03) respectively and RI 60% and 30% respectively. For patients in stable/progressive disease LFS was 40% and 55% (p=0.10) and RI 52% and 37% (p=0.07) respectively. By multivariate analysis a trend for a lower RI was associated to in vitro purging (p=0.08, HR:0.63). Study of interactions between purging and prognostic factors showed that purging and PR status at time of ASCT was associated to a lower RI (p=0.06, HR:0.32). These results indicates that there might be a benefit of in vitro purging in some patients with B CLL according to their status at transplant.

1/7/40
DIALOG(R)File 5:Biosis Previews(R)

0015546362 BIOSIS NO.: 200510240862
Weekly dose-dense cisplatin-epirubicin-paclitaxel administration with granulocyte colony-stimulating factor support does not substantially improve prognosis in extensive disease small-cell lung cancer - A SICOG phase II study
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JOURNAL: Oncology (Basel) 68 (2-3): p223-229 2005 2005
ISSN: 0030-2414
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ABSTRACT: Purpose: The present study was aimed at defining the antitumor activity of the cisplatin-epirubicin-paclitaxel (PET) weekly administration with granulocyte colony-stimulating factor (G-CSF) support in chemonaive small-cell lung cancer patients with extensive disease (ED-SCLC). Methods: Chemonaive ED-SCLC patients received cisplatin 30 mg/sqm, epirubicin 50 mg/sqm and paclitaxel 120 mg/sqm, weekly, with G-CSF (5 mu g/kg from day 3 to 5) support, for a maximum of 12 weeks. Results: Thirty-nine patients were treated, for a total of 354 cycles delivered. Eight complete (21%), and 22 partial responses (56%) were recorded, giving a 77% (95% CI=61-89%) objective response rate (ORR). After 14 (range, 7-%28%)-month median follow-up, 24 deaths have occurred. Median progression-free and overall survival were 7 months and 11 months, with 1- and 2-year projected survivals of 45 and 24%, respectively. No

toxic deaths occurred. Grade 4 neutropenia and thrombocytopenia occurred in 4 (10%) and 1 (3%) patients, respectively. Only one case of neutropenic sepsis was recorded, while hemorrhagic thrombocytopenia was never observed. Emesis, loss of appetite, mucositis and fatigue were the main nonhematological toxicities, being severe in 9, 8, 4 and 7 patients, respectively. Conclusions: The weekly PET combination with G-CSIF support represents ân active therapeutic approach in chemonaive ED-SCLC patients. However, both ORR and median survival does not seem substantially better than those achievable with a standard regimen. In view of that, and in consideration of the relevant nonhematological toxicity, this approach should not be pursued outside clinical trials. Copyright (C) 2005 S. Karger AG, Basel.

1/7/41
DIALOG(R)File 5:Biosis Previews(R)

0015500581 BIOSIS NO.: 200510195081
Prevention of left ventricular remodeling with granulocyte colony-stimulating factor after acute myocardial infarction - Final 1-year results of the front-integrated Revascularization and stem cell liberation in evolving acute myocardial infarction by granulocyte colony-stimulating factor (FIRSTLINE-AMI) trial
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JOURNAL: Circulation 112 (9, Suppl. S): pI73-I80 AUG 30 2005 2005
ISSN: 0009-7322
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ABSTRACT: Background-Experimental and clinical evidence has recently shown that pluripotent stem cells can be mobilized by granulocyte colony-stimulating factor (G-CSF) and may enhance myocardial regeneration early after primary percutaneous coronary intervention (PCI) management of acute myocardial infarction. Sustained or long-term effects of mobilized CD34-positive mononuclear stem cells, however, are unknown.Methods and Results-Thirty consecutive patients with ST-elevation myocardial infarction undergoing primary PCI with stenting and abciximab were selected for the study 85 +/- 30 minutes after PCI; 15 patients were randomly assigned to receive subcutaneous G-CSF at 10 mu g/kg body weight for 6 days in addition to standard care including aspirin, clopidogrel, an angiotensin-converting enzyme inhibitor, P-blocking agents, and statins. In patients with comparable demographics and clinical and infarct-related characteristics, G-CSF stimulation led to sustained mobilization of CD34 positive mononuclear cells (MNCCD34+), with a 20-fold increase (from 3 +/- 2 at baseline to 66 +/- 54 MNCCD34+/mu L on day 6; P<0.001); there was no evidence of leukocytoclastic effects, accelerated restenosis rate, or any late adverse events. Within 4 months, G-CSF-induced MNCD34+ mobilization led to enhanced resting wall thickening in the infarct zone of 1.16 +/- 0.29 mm (P<0.05 versus control), which was sustained at 1.20 +/- 0.%28% after 12 months (P < 0.001 versus control). Similarly, left ventricular ejection fraction improved from 48 +/- 4% at baseline to 54 +/- 8% at 4 months (P < 0.005 versus control) and 56 +/- 9% at 12 months (P < 0.003 versus control and paralleled by sustained improvement of wall-motion score index from 1.70 +/- 0.22 to 1.42 +/- 0.26 and 1.33 +/- 0.21 at 4 and 12 months, respectively), after G-CSF (P<0.05 versus baseline and P < 0.03 versus controls). Accordingly, left ventricular end-diastolic diameter showed no remodeling and stable left ventricular dimensions after G-CSF stimulation, whereas left ventricular end-diastolic diameter in controls revealed enlargement from 55 4 mm at baseline to 58 4 mm (P<0.05 versus baseline) at 12 months after infarction and no improvement in diastolic function.Conclusion-Mobilization of MNCD34+ by G-CSF after primary PCI may offer a pragmatic strategy for improvement in ventricular function and prevention of left ventricular remodeling I year after acute myocardial infarction.

1/7/42
DIALOG(R)File 5:Biosis Previews(R)

0015300506 BIOSIS NO.: 200500204308
Effect of recombinant human GH on circulating granulocyte colony-stimulating factor and neutrophils in patients with adult GH deficiency
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JOURNAL: European Journal of Endocrinology 152 (2): p211-215 February 2005 2005
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ABSTRACT: Background: We previously reported that short-term continuous subcutaneous infusion (CSI) of recombinant human growth hormone (rhGH) increased plasma erythropoietin levels and hemoglobin concentrations in the effect of rhGH on plasma granulocyte colony-stimulating factor (G-CSF) levels and neutrophil counts in patients with adult GH deficiency. Methods: rhGH was administrated for 1 year in six patients with adult GH deficiency (age range, 24-69 years; mean +/- S.E.M., 51.7 +/- 5.8 years; two males and four females) by means of CSI at a rate of 0.25 U/kg per week. Blood samples were obtained in the morning after overnight fasting every month before and after the start of rhGH administration. Plasma GH, insulin-me growth factor I (IGF-I) and G-CSF levels, and neutrophil counts, were measured. Results: Mean (+/-S.E.M.) plasma GH levels increased from 0.26 +/- 0.14 to 2.%28% +/- 0.20 mug/l 1 month after the start of rhGH administration. An increase of the plasma GH levels was accompanied by an increase in the plasma IGF-I levels from 64.7 +/- 8.5 to 293.3 +/- 80.6 mug/l. Plasma G-CSF levels increased at 2, 3, 8, 9 and 10 months after the start of rhGH administration compared with %28%.6 +/- 11.0 ng/l at time 0. The neutrophil counts increased at 2, 3, 7, 8, 9, 11 and 12 months after the start of rhGH administration compared with 2 8 2 2 3 7 7 neutrophils/ mul at time 0. Conclusion: rhGH administration increased plasma G-CSF levels and neutrophil counts. GH and/or IGF-I might stimulate neutrophil production and/or release via G-CSF.

1/7/43
DIALOG(R)File 5:Biosis Previews(R)

0015287629 BIOSIS NO.: 200500194694
ESHAP plus G-CSF as an effective peripheral blood progenitor cell mobilization regimen in pretreated non-Hodgkin's lymphoma: comparison with high-dose cyclophosphamide plus G-CSF
AUTHOR: Lee J-L; Kim S; Kim S W; Kim E-K; Kim S-B; Kang Y-K; Lee J; Kim M W ; Park C J; Chi H-S; Huh J; Kim S-H; Suh C (Reprint)
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) regimen has been shown to be effective as an active salvage therapy for lymphoma. Mobilizing stem cells following ESHAP should decrease time to transplantation by making separate mobilizing chemotherapy (MC) unnecessary, while controlling a patient's lymphoma. We therefore assessed the mobilization potential of ESHAP plus G-CSF in 26 patients (ESHAP group) with non-Hodgkin's lymphoma (NHL) and compared these results with those of 24 patients with NHL who received high-dose (4 g/m2l) cyclophosphamide (HDCY) as MC (HDCY group). The age, sex, and radiotherapy to the axial skeleton were well matched between groups, but the number of patients with poor mobilization predictors was higher in the ESHAP group. Significantly higher numbers of CD34+ cells (x 106/kg) (%17%.1 +/- 18.8 vs 5.8 +/- 5.0, P = 0.03) and apheresis day 1 CD34+ cells (x 106/kg) (5.5 +/- 6.6 vs 1.7 +/- 2.0, P = 0.014) were collected from the ESHAP group than from the HDCY group, and the number of patients who achieved an optimal CD34+ cell target of 5 x 106/ kg was higher in the ESHAP group (81 vs 50%, P = 0.022). Log-rank test revealed that time to target peripheral blood progenitor cell collection (gtoreq 5 x 106/kg) was shorter in the ESHAP group (P = 0.007). These results indicate that ESHAP plus G-CSF is an excellent mobilization regimen in patients with relapsed and poor-risk aggressive NHL.

1/7/44
DIALOG(R)File 5:Biosis Previews(R)

0015287628 BIOSIS NO.: 200500194693
Hematopoietic stem cell mobilization with intravenous melphalan and G-CSF in patients with chemoresponsive multiple myeloma: report of a phase II trial
AUTHOR: Gupta S; Zhou P; Hassoun H; Kewalramani T; Reich L; Costello S; Drake L; Klimek V; Dhodapkar M; Teruya-Feldstein J; Hedvat C; Kalakonda N ; Fleisher M; Filippa D; Qin J; Nimer S D; Comenzo R L (Reprint)
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JOURNAL: Bone Marrow Transplantation 35 (5): p441-447 March 2005 2005
MEDIUM: print
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ABSTRACT: Multiple myeloma (MM) is an incurable hematologic malignancy for which autologous hematopoietic stem cell transplantation (HCT) is a standard therapy. The optimal method of stem cell mobilization is not defined. We evaluated intravenous melphalan (60 mg/ m2), the most effective agent for MM, and G- CSF (10 mug/ kg/ day) for mobilization. End points were safety, adequacy of CD34+ collections, MM response, and contamination of stem cell components (SCC). In total, 32 patients were mobilized. There were no deaths or significant bleeding episodes; 14 patients (44%) required hospitalization for neutropenic fever. Median days of grade 3 or 4 neutropenia or thrombocytopenia were 7 (2 - 20) and 8 (3 - %17%). Median mobilization days, CD34+ cells/ kg and total leukaphereses were 16 (12 - 30), 12.1 million (2.6 - 52.8), and 2 (1 - 5) respectively. Four patients (12.5 %) failed to achieve the target of 4 million CD34+ cells/ kg in five leukaphereses. Reduction in myeloma was seen in 11 patients (34%) wit h 3 (9%) achieving complete response; 15 (47%) maintained prior responses. Estimated MM contamination per SCC (N = 48) was 0.0009% (range 0 - 0.1) and 0.21 x 10 4 cells per kg (range 0 - 41.2). Increased contamination was associated with increased patient age. This strategy for mobilization is feasible, frequently requires hospitalization and transfusion, and controls disease in most patients.

1/7/45
DIALOG(R)File 5:Biosis Previews(R)

0015266674 BIOSIS NO.: 200500173410
Fludarabine-based conditioning for allogeneic stem cell transplantation for multiply transfused patients with Fanconi's anemia
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ABSTRACT: A fludarabine-based protocol (fludarabine (25 mg/m2/ day x 6 days), cyclophosphamide (10 mg/kg/day x 2 days) and ATG (ATGAM 10 mg/kg/day x 4 days)) was used in four multiply transfused Fanconi's anemia (FA) patients aged 5 - 15 years to reduce rejection during allogeneic bone marrow transplantation (BMT). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and mini methotrexate. The graft source was G-CSF-stimulated bone marrow or peripheral blood stem cells (PBSC) in two patients each. All patients engrafted with median time to ANC >500/mm3 being 14 days (range: 12 - %17%) and unsupported platelet count >20,000/mm3 being 13 days (range: 11 - 18). One patient had secondary graft rejection on day 56 and expired on day 69 due to fungal pneumonia. One patient who developed acute myeloid leukemia on day 56 underwent successful induction with cytosine and daunorubicin followed by peripheral blood stem cell (PBSC) rescue on day 70 and is presently in remission with complete donor chimerism and grade I GVHD. At a median follow-up of 13 months (range: 4 - 21), three patients (75%) are well with complete donor chimerism. Addition of fludarabine to the conditioning regimen for BMT in FA can provide additional immunosuppression for engraftment without increasing toxicity.

1/7/46
DIALOG(R)File 5:Biosis Previews(R)

0015203883 BIOSIS NO.: 200500120948
Th1 shift in CIDP versus Th2 shift in vasculitic neuropathy in CSF
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ABSTRACT: To investigate the intra- and extracellular levels of various cytokines and chemokines in CSF in chronic inflammatory demyelinating polyneuropathy (CIDP) and vasculitic neuropathy (VN), 16 cytokines, IL-1beta, IL-2, 11-4, IL-5, IL-6, IL-7, IL-8, IL-10, 11-12 (p70), IL-13, IL-%17%, IFN-gamma, TNF-alpha, G-CSF, MCP-1 and MIP-1beta, were measured in CSF supematant by a multiplexed fluorescent bead-based immunoassay and intracellular production of IFN-gamma and IL-4 in CSF CD4+ T cells were simultaneously measured by flow cylonveiry, in 14 patients with CIDP, 8 patients with VN and 25 patients with other noninflammatory neurologic diseases (OND). In the CSF supematant, a significant increase of IL-%17%, IL-8 and IL-6, and a significant decrease of 11-4. IL-5 and IL-7 levels were detected in pretreated CIDP as compared with OND. A significant increase of IL-6, IL-8 and IL-10 levels was found in pretreated VN. Both IL-7 and IL-8 levels correlated strongly with CSF protein levels in CIDP. although the correlation of IL-6 levels was weak. In CSF CD4+ T cells

IFN-gamma+ IL-4+ cell percentages were markedly elevated in CIDP compared with OND, but not in VN. resulting in a significant increase of intracellular IFN-gamma/IL-4 ratio in CIDP, even in the absence of CSF pleocytosis. The nonresponders to intravenous immunoglobulins (IVIGs) showed a significantly lower IFN-gamma- IL-4+ CD4+ T cell percentage, and tended to have a higher intracellular IFN-gamma/IL-4 ratio than the responders in CSF. Marked upregulation of Th1 cytokine, IL-%17%. and downregulation of Th2 cytokines, together with infiltration of IFN-gamma-producinq CD4+ T are useful markers for CIDP, while several Th2 cytokines are upregulated in VN in CSF. Copyright 2004 Elsevier B.V. All rights reserved.

1/7/47
DIALOG(R)File 5:Biosis Previews(R)

0015137539 BIOSIS NO.: 200500044289
Suppressing effects of dietary supplementation of soybean trypsin inhibitor on spontaneous, experimental and peritoneal disseminated metastasis in mouse model
AUTHOR: Kobayashi Hiroshi (Reprint); Fukuda Yoichi; Yoshida Ryuji; Kanada Yasufumi; Nishiyama Setsuko; Suzuki Mika; Kanayama Naohiro; Terao Toshihiko
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JOURNAL: International Journal of Cancer 112 (3): p519-524 November 10, 2004 2004
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ABSTRACT: The modifying effects of a Kunitz trypsin inhibitor (KTI) and a Bowman-Birk trypsin inhibitor (BBI), purified from soybean trypsin inhibitor, as dietary supplements on experimental and spontaneous pulmonary metastasis of murine Lewis lung carcinoma 3LL cells as well as peritoneal disseminated metastasis model in human ovarian cancer HRA cells were investigated in i.v., s.c. and i.p. injection models in mice. Seven groups of female C57BL/6 or nude mice were fed a basal diet (control group) or the basal diet supplemented with KTI or BBI (5, 15, or 50 g/kg). Here we show that, in an in vivo spontaneous metastasis assay, the diet supplementation with KTI (15 and 50 g/kg), but not with BBI, for %28% days immediately after s.c. tumor cell inoculation significantly inhibited the formation of lung metastasis in C57BL/6 mice in a dose-dependent manner. The inhibition of lung metastasis was not due to direct antitumor effects of KTI. In an in vivo experimental metastasis assay, the diet supplementation with KTI or BBI for 21 days after i.v. tumor cell inoculation did not reduce the number of lung tumor colonies. In addition, KTI (15 or 50 g/kg) treatment in a peritoneal disseminated metastasis model of HRA cells resulted in a 40% reduction in total tumor burden when compared with control animals. Immunoblot analysis revealed that KTI specifically reduced expression of uPA protein as well as phosphorylation of MAP kinase and P13 kinase proteins in the cells stimulated with agonists (G-CSF for 3LL cells or TGF-beta1 for HRA cells). These results suggest that dietary supplementation of KTI more efficiently regulates the mechanism involved in the entry into vascular circulation of tumor cells (intravasation) than in extravasation during the metastatic process. KTI treatment may also be beneficial for ovarian cancer patients with or at risk for peritoneal disseminated metastasis; it greatly reduces tumor burden in part by inhibiting phosphorylation of MAP kinase and P13 kinase, leading to suppression of uPA expression. Copyright 2004 Wiley-Liss, Inc.

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DIALOG(R)File 5:Biosis Previews(R)

0015129295 BIOSIS NO.: 200500036360
Combined administration of alpha-erythropoietin and filgrastim can improve the outcome and cost balance of autologous stem cell transplantation in patients with lymphoproliferative disorders
AUTHOR: Olivieri A (Reprint); Scortechini I; Capelli D; Montanari M; Lucesole M; Gini G; Troiani M; Offidani M; Poloni A; Masia M C; Raggetti G M; Leoni P
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JOURNAL: Bone Marrow Transplantation 34 (8): p693-702 October 2004 2004
MEDIUM: print
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ABSTRACT: We compared the use of G-CSF plus EPO in a group of 32 multiple myeloma and lymphoma patients with historical controls receiving G-CSF alone. Haemopoietic reconstitution was significantly faster in patients receiving G-CSF+EPO(group B), with a median time of 10 days to achieve an ANC count >0.5 x 109/l, compared to 11 days in the historical group (A). The median duration of severe neutropenia (ANC count 100/ml) was significantly shorter in group B compared to group A; platelet counts >20 x 109 and >50 x 109/l were achieved at days +13 and +%17%, respectively in group B, compared to days +14 and +24, respectively, in group A (P = 0.015, 0.002) patients. The transfusion requirement was reduced in group B, with 0 (0 - 6) RBC units and 1 (0 - 5) platelet unit transfused in group B vs 2 RBC (0 - 9) and 2 platelet units (0 - 8) in group A. Median days of fever, antibiotic therapy and hospital stay were reduced in group B (9.5 days vs 22). The mean cost of autotransplantation per group A patient was 23 988 Euro, compared with 18 394 Euro for a group B patient. Our study suggests that the EPO+G-CSF combination not only accelerates engraftment kinetics, but can also improve the clinical course of ASCT.

1/7/49
DIALOG(R)File 5:Biosis Previews(R)

0015023242 BIOSIS NO.: 200400394031
A randomised study comparing peripheral blood progenitor mobilisation using intermediate-dose cyclophosphamide plus lenograstim with lenograstim alone
AUTHOR: Karanth M; Chakrabarti S; Lovell R A; Harvey C; Holder K; McConkey C C; McDonald D; Fegan C D; Milligan D W (Reprint)
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JOURNAL: Bone Marrow Transplantation 34 (5): p399-403 September 2004 2004
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ABSTRACT: We conducted a prospective randomised study to compare the efficiency of out-patient progenitor cell mobilisation using either intermediate-dose cyclophosphamide (2 g/m2) and lenograstim at 5 mug/kg (Cyclo-G-CSF group, n = 39) or lenograstim alone at 10 mug/kg (G-CSF group, n = 40). The end points were to compare the impact of the two regimens on mobilisation efficiency, morbidity, time spent in hospital, the number of apheresis procedures required and engraftment kinetics. Successful mobilisation was achieved in %28%/40 (70%) in the G-CSF group vs 22/39 (56.4%) for Cyclo-G-CSF (P = 0.21). The median number of CD34+ cells mobilised was 2.3 x 106/kg and 2.2 x 106/kg for G-CSF and cyclo-G-CSF arms following a median of two apheresis procedures. Nausea and vomiting and total time spent in the hospital during mobilisation

were significantly greater after Cyclo-G-CSF (P 0.05). Rapid neutrophil and platelet engraftment was achieved in all transplanted patients in both groups. In conclusion, G-CSF at 10 mug/kg was as efficient at mobilising progenitor cells as a combination of cyclophosphamide and G-CSF with reduced hospitalisation and side effects and prompt engraftment. When aggressive in-patient cytoreductive regimens are not required to both control disease and generate progenitor cells, the use of G-CSF alone appears preferable to combination with intermediate-dose cyclophosphamide.

1/7/50
DIALOG(R)File 5:Biosis Previews(R)

0015018285 BIOSIS NO.: 200400389074
Low-dose lenograstim to enhance engraftment after autologous stem cell transplantation: a prospective randomized evaluation of two different fixed doses
AUTHOR: Suh Cheolwon (Reprint); Kim Hyo-Jung; Kim Sang-Hee; Kim Shin; Lee Soon-Jong; Lee Yoon-Shin; Kim Eun-Kyoung; Kim Sung-bae; Lee Jung-Sin; Kim Michael W; Kim Kihyun; Yoon Sung-Soo
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JOURNAL: Transfusion (Malden) 44 (4): p533-538 April 2004 2004
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LANGUAGE: English

ABSTRACT: BACKGROUND: G-CSF is used to enhance hematopoietic recovery after autologous stem cell transplantation (ASCT), but the optimal dose of G-CSF during engraftment has not been established. The medical cost of ASCT is a serious financial burden in developing countries, and G-CSF is the most costly drug used in this procedure. We evaluated whether a lower, vial-size fitted dose of lenograstim is clinically equivalent to a higher fixed dose. STUDY DESIGN AND METHODS: A prospective randomized study was performed on 33 patients (11 non-Hodgkin's lymphoma, 8 multiple myeloma, 14 breast cancer) undergoing ASCT Patients were randomly administered 100 mug or 250 mug lenograstim daily starting on the next day of ASCT, with a minimum infusion of 3 x 106 CD34+ cells per kg. RESULTS: For both lenograstim doses, median time to neutrophil engraftment was 9 days and median time to PLT engraftment was 11 days. Episodes of clinically documented infections were 10 per 379 patient-days in the 100 mug per day group and 10 per 320 patient-days in the 250 mug per day group. There were no between-group differences in requirements for transfusion of RBCs or PLTs. Duration of hospitalization was 16 days for the 100 mug per day group and %17% days for the 250 mug per day group. Daily lenograstim dose per patient's body weight and total amount of lenograstim used during ASCT were both significantly lower in the 100 mug per day group. CONCLUSION: Administration of 100 mug per day of lenograstim showed comparable clinical efficacy to 250 mug per day lenograstim for immediate hematopoietic recovery after ASCT. Use of the lower dose was associated with lower overall lenograstim usage and lower cost.

1/7/51
DIALOG(R)File 5:Biosis Previews(R)

0014916546 BIOSIS NO.: 200400287303
Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-%17%
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JOURNAL: FASEB Journal 18 (4-5): pAbst. 559.5 2004 2004
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LANGUAGE: English

ABSTRACT: Neutrophil production closely matches elimination to maintain approximately constant numbers in the blood circulation. A homeostatic mechanism has been proposed to regulate this process, but was never demonstrated. Here we show that phagocytosis of apoptotic neutrophils by macrophages and dendritic cells reduces IL-%17% production <I>in vitro</I> and <I>in vivo</I>, which subsequently curbs G-CSF mediated granulopoiesis. IL-%17% mRNA expression is highest in the mesenteric lymph node in WT mice. Intracellular staining for IL-%17% reveals that both γδ T cells and an unconventional population of αβ T cells account for this IL-%17% production. IL-23 is known to stimulate IL-%17%. Phagocytosis of apoptotic neutrophils by dendritic cells or macrophages drastically reduces their IL-23 production. To directly demonstrate the importance of the proposed mechanism <I>in vivo</I>, we show that adoptively transferred bone marrow-derived WT neutrophils transiently correct the neutrophilia in CD18-/- mice and cause a concomitant drop in IL-%17% production. Our data show that phagocytosis of apoptotic neutrophils reduces IL-23 production in macrophages and dendritic cells and subsequent secretion of IL-%17% and G-CSF, thus establishing a homeostatic mechanism for the regulation of neutrophil production. Supported by NIH HL-54136 K.L. and T32 GM 08715-01A1 M.A.S. .

1/7/52
DIALOG(R)File 5:Biosis Previews(R)

0014814475 BIOSIS NO.: 200400182161
Retroviral gene transfer of cytidine deaminase into human hematopoietic cells.
AUTHOR: Lehmberg Kai (Reprint); Rattmann Ina (Reprint); Bardenheuer Walter (Reprint); Schneider Axel (Reprint); Seeber Siegfried (Reprint); Moritz Thomas (Reprint); Flasshove Michael (Reprint)
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JOURNAL: Blood 102 (11): p497b November 16, 2003 2003
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CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
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LANGUAGE: English

ABSTRACT: Transfer of human cytidine deaminase (CDD) into murine hematopoietic progenitor cells has been shown to confer resistance to cytarabin (ara-C) and related compounds such as gemcitabine in vitro and in vivo, but data on the transfer of CDD into primary human hematopoietic cells have not been reported, thus far. Therefore, we constructed a retroviral vector based on the hybrid SFFV/MESV backbone expressing CDD upstream and the enhanced green fluorescent protein (EGFP) downstream of an internal ribosomal entry site. Stably transduced PG13 cells were sorted by FACS to select for EGFP producing single cell clones and cell-free retroviral supernatant from these clones was used to transduce CD34-selected and IL-3/SCF/IL-6 prestimulated human umbilical cord blood (UCB) cells. A vector expressing EGFP only served as a mock control. Retroviral transduction resulted in 27.8+-1.5% EGFP+ cells (n=4, mean+-SEM). Functional CDD expression was assessed as resistance of

transduced progenitor cells to ara-C in a clonogenic assay. The percentage of surviving colony-forming units (CFU-C) significantly increased from 38.9+-9.4% to 59.1+-6.0% at a concentration of 30 nM ara-C, from %17%.7+-5.0% to 38.5+-8.0% at 60 nM ara-C, and from 8.6+-3.7% to 22.6+-6.4% at 100 nM ara-C ($p<0.01$; n=5-6). The LD50 for CFU-C significantly increased from 26.9+-6.0 to 48.6+-9.2 nM ara-C ($p<0.05$; n=5). For the subset of BFU-E the protection was even more pronounced. PCR amplification of proviral sequences and subsequent Southern blotting confirmed the presence of vector DNA in transduced colonies. In addition, prestimulated and transduced CD34+ UCB cells were selected in liquid culture in the presence of ara-C and IL-3/SCF/IL-6/G-CSF. Selection in 30 nM ara-C resulted in a 1.4 fold and 2.5 fold increase in the percentage of EGFP+ cells after 4 and 8 days, respectively. In summary, retroviral transfer and expression of the drug resistance gene CDD in primary human hematopoietic conferred ara-C resistance to clonogenic progenitor cells and allowed in vitro selection of successfully transduced cells.

1/7/53
DIALOG(R)File 5:Biosis Previews(R)

0014814426 BIOSIS NO.: 200400182112
Clinical report on the treatment of Chinese children with advanced malignant solid tumors with autologous haematopoietic stem cell transplantation.
AUTHOR: Chen Jing (Reprint); Wang Yaoping (Reprint); Tang JingYan (Reprint) ; Zhao Huijun (Reprint); Pan Ci (Reprint); Xue Huiliang (Reprint); Gu LongJun (Reprint)
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JOURNAL: Blood 102 (11): p485b November 16, 2003 2003
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SPONSOR: American Society of Hematology
ISSN: 0006-4971
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LANGUAGE: English

ABSTRACT: To improve the therapeutic efficacy in children with malignant solid tumors at high risk, %28% times of autolougs haematopoietic stem cell transplantation have been performed in 27 children with advanced solid tumors. The bone marrow was collected from the anterior crista of iliac in both side in 13 cases while peripheral mononuclear cell was harvested with CS-3000 cell seperator in other 15 patients after G-CSF mobilization. As one of them suspected to have bone marrow involvement of the neuroblastoma, the autograft in this case was purged with CliniMACS based on the CD34 positive selection. In addition to 2 children with Hodgkin's disease conditioned with CBV protocol (Cyclophosphamide+BCNU+Etopside), all other children conditioned with Etopside plus Carboplatin plus Melphalan. Results showed the number of mononuclear cell collected from bone marrow or peripheral blood was equal to 5.4+-2.1X108/kg and 4.1+-1.9X108/kg respectively. All of them achieved the haematopoietic reconstitution after transplantation. The mean time for the neutrophile count recovering to 0.5X109/L was 11.8+-5.7 days and the platelet recovering over 2.0X109/L was 21.0+-9.3 days with average 3 units of packed red blood cells and 3 units of platelet products transfused in the course of transplantation. 12 children complicated neutropenia and fever. 3 of them had positive results from blood culture including staphylococcus epidermal, staphylococcus saprophyte and bacillus subtilis respectively. None of our children died of complication associated with transplantation. But one child complicated acute renal failure, pulmonary edema and pericardial effusion followed by respiratory distress syndrome, with the active comprehensive treatment of mechanical ventilation and pulmonary surface active factor etc. This child recovered at last. In another one child, BCNU associated pulmonary injury occurred leading to severe pulmonary hypertension, eosinophilosis, but with the treatment of corticosteroid and other drugs, this child also gradually recovered. The mean fellow up time was 13 months in this group of patients. 4/27 children died of relapse 5 months after transplantation. 1/27 child with NHL had CNS involvement 3 months after transplantation. But up to now, this child has kept on surviving with tumor for %17% months. Other 22 children still in the disease-free survival indicating that autologous stem cell transplantation is a safe and effective measure in saving the life of children with malignant solid tumors and worth of further recommendation.

1/7/54
DIALOG(R)File 5:Biosis Previews(R)

0014814422 BIOSIS NO.: 200400182108
Continuous intravenous infusion idarubicin and busulphan as conditioning for elderly patients with acute myeloid leukemia undergoing autologous stem cell transplantation: A feasibility Study.
AUTHOR: Ferrara Felicetto (Reprint); Palmieri Salvatore (Reprint); Mele Giuseppina (Reprint); Pocali Barbara (Reprint); Schiavone Ettore Mariano (Reprint); Annunziata Mario (Reprint); De Simone Maria Carla (Reprint); Califano Catello; D'Arco Alfonso M (Reprint)
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JOURNAL: Blood 102 (11): p484b November 16, 2003 2003
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CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
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LANGUAGE: English

ABSTRACT: The prognosis of acute myeloid leukemia (AML) is poor in the elderly due to low complete remission (CR) rate and high relapse rate. Aiming at reducing relapse, autologus stem cell transplantation (ASCT) is increasingly used in older AML patients. However, toxicity is considerable and relapse rate remains high after conditioning with the classical combination of Busulphan (Bus) and Cyclophosphamide. In young/adult patients, we previously demonstrated the feasibility of an original conditioning regimen, called IBu, consisting of a combination of high dose Idarubicin (IDA) administered at 20 mg/m2/day as continuous infusion (ci) from day -13 to -11, followed by oral Bus at 4 mg/kg/day form day -5 to -2. Here we report data from a series of 13 AML patients conditioned to ASCT with a reduced schedule of IBu regimen, (ci IDA at 20 mg/m2/day from day -12 to -11 and oral Bu at 4 mg/kg/day from day -4 to -2), specifically designed for elderly patients. Patients with acute promyelocytic leukemia (APL) in CR1 were excluded. 13 patients received ASCT, after conditioning with IBu. The median age was 64 years (61-74); 11 (85%) were autografted in CR1, 2 in CR2, including 1 APL. Among CR1 patients, 8 had normal karyotype, 3 complex karyotype; as concerns CR2, the patient with APL had t(15;%17%), one had 6p- and one complex karyotype. All transplants were performed in single or double conventional rooms using peripheral blood stem cells (PBSC) collected after consolidation followed by G-CSF. Prophylaxis against infection consisted of oral cyprofloxacin, while neither antiviral nor antifungal prophylaxis were adopted. The median number of CD34 positive cells infused was 5.6X106/kg (2.5-19). In all patients left ventricular ejection fraction (LVEF) was evaluated before and after ASCT. All patients experienced full engrafment. The median number of days for stable recovery of neutrophils to 0.5X109/L and platelets to 20X109/L was 11 (9-19) and 12 (6-38), respectively. The median number of platelet and blood units transfused was 3 (1-7) and 4 (1-5), respectively. The only episodes of WHO grade 3-4 extra-hematological toxicity consisted of stomatitis requiring total parenteral nutrition in 9 patients (69%) and resolved at the time of hematopoietic recovery. Fever occurred in 12 patients; there were 10 cases of fever of unknown origin and two documented infections, one bacterial pneumonitis and one pulmonary

aspergillosis, both resolved with antibiotic and antifungal therapy after hematopoetic recovery. There was no case of transplant related mortality; of note, LVEF examination post-ASCT did not reveal cardiac toxicity in any patient. At the time of writing with a median follow up of 12 months (range 2-46), 9 patients are in continuous CR1, while 3, two of which autografted in CR2, have relapsed at 3, 6, and 8 months from ASCT, respectively, and have died from progressive disease. One patient died from gastric cancer, while in CR1. Median overall and disease free survival have not yet been reached after a median follow up of 12 months from transplantation and 16 months from diagnosis. In conclusion, our data demonstrate acceptable toxicity of the combination of idarubicin plus busulphan as conditioning to ASCT in elderly AML patients and suggest a possible reduction of relapse rate. These very encouraging results need to be confirmed in a larger series with longer follow-up.

1/7/55
DIALOG(R)File 5:Biosis Previews(R)

0014814419 BIOSIS NO.: 200400182105
Feasibility of autologous stem cell transplantation in elderly patients with acute myeloid leukaemia treated with continuous sequential infusion of fludarabine plus cytarabine (CI-FLA).
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ABSTRACT: Autologous stem cell transplantation (ASCT) is increasingly used in acute myeloid leukemia (AML); however, due to toxicity of induction/consolidation treatment, early relapse and insufficient collection of CD34+ cells, ASCT is given to a small minority of older patients. We investigated the feasibility of ASCT from a series of 44 newly diagnosed patients, treated with combination of fludarabine (F) plus cytarabine (ARA-C) given as continuous sequential infusion. Patients were required to have non M3 AML and age more than 60. F was given at a loading dose of 10 mg/m2 over 15 min at day 0 followed by a continuous infusion (CI) of 20 mg/m2/24 hours for 72 hours, ARA-C at a loading dose of 390 mg/m2 over 15 min three hours and half after F and then as CI over 96 hours at 1440 mg/24 hours for a total of 96 hours. G-CSF was added at day +15 at 5mg/kg. Patients in complete remission (CR) were programmed to receive an additional identical course of CI-FLA. However, after the first 20 patients, consolidation was reduced by one day because of excessive toxicity. Following consolidation, G-CSF at 10 mg/kg was given from day +15 in order to shorten neutropenia and mobilize CD34+ cells. 44 patients (median age 69 years, range 61-81) received the therapeutic program. In %17% patients (39%) a previously diagnosed myelodysplastic syndrome (MDS) preceded the onset of AML, while in 9 (20%) multilinear dysplastic abnormalities were present in apparently de novo cases. Among 36 patients with evaluable cytogenetics (82%), %17% had normal karyotype (47%), 12 complex karyotype (33%) and 7 other chromosomal abnormalities (19%); 38 patients (86%) were affected by concomitant disease requiring specific treatment. Overall, %28% patients achieved CR (64%), all after one course of CI-FLA. There were 8 induction deaths (18%), while 8 patients (18%) were refractory to induction. All patients experienced febrile neutropenia requiring broad spectrum empiric antibiotic and/or antifungal therapy as well as platelet and blood transfusions. Among remitters, 23 out of %28% patients received the programmed consolidation course, while in 5 cases (11%) therapy was discontinued due to induction toxicity. Following consolidation, 16 patients were monitorized for the mobilization of CD34+ cells, collection being successful in 11 (69%). The median number of CD34+ cells collected was 9.%17% (2.5-42.7), after a median number of 2 aphereses. Overall, 8 patients (18%) have received ASCT, the only reason for exclusion being early relapse. Toxicity of ASCT was acceptable with no case of transplant related mortality. In conclusion, this study demonstrates that continuous sequential infusion of F+ARA-C is an effective and relatively well-tolerated regimen for elderly patients with AML. The collection of CD34+ cells is successful in 69% of eligible cases while ASCT is feasible in 73% of mobilizing patients, the only reason of exclusion being early relapse. Overall, 8 out of 44 patients (18%) were actually given ASCT, These results compare favorably with anthracyclines+ARA-C in terms of CD34+ cell collection and feasibility of ASCT in AML of the elderly. Toxicity of induction/consolidation treatment and early relapse remain the major obstacle for ASCT.

1/7/56
DIALOG(R)File 5:Biosis Previews(R)

0014814412 BIOSIS NO.: 200400182098
The autogeneic peripheral blood haemopoietic stem cells transplantation for treatment of the chronic myeloid leukemia after Ph chromosome negative by STI 571.
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ABSTRACT: Objective: To study the possibility of chronic myeloid leukemia will be cured by autogeneic hamatologic stem cells transplantation after Ph chromosome negative by STI 571. Methods: Among the three patients with chronic myeloid leukemia have two male and one females and the ages was from %28% to 46 years old. Both of the Ph chromosome positive cells and bcr/abl fusion genes positive cells detected by FISH were gtoreq90% before treatment with STI 571. All of them was administrated oral STI 571 daily at a dose from 300mg to 400mg for 5 months to 8 months. The all of Ph chromosom and FISH-bcr/abl were complete negative in 3 time detectation after treatment 3 months. The course disease from diagnosis to the transplantation was from 4 months to 12 months. The peripheral blood haemapoietic stem cells was mobilized by the regimes that is consist of the cytarabine 2.0 daily for 3 days. Etoposide 0.2 daily for 3 days and cyclophosphamide 1.0 daily for one day. All of them were administrated intravenously. When white blood cell was less than 1.0X109/L the G-CSF 300mug daily was subcutaneously for 5 days or 6 days and then the mononuclear cells was received by Cs-3000 pluse. The bcr/abl fusion genes positive cells rate from CD34 positive cells purified by miniMAC in the products was arrange 11% from 14%. After 3 weeks the patients total body irradiation was 9.0 Gy different two time and they were administrated by Cyclophosphamide 60mg/kg daily intravenously for two days and Etoposide 0.3 daily intravenously for 2 days. After this, They was intravenously MNC 4.0apprx5.2X108/kg. IL-2 was administrated daily at dose 107 unit subcutaneously from 0 day to +13 days. G-CSF was administrated at dose 300mug daily subcutaneously from +3 to +12 days. Result: ANC >0.5X109/L from three patients spend 9apprx12 days, Pletelet count >20X109/L from them spend 8apprx21 days. The 2 of three patients showed cytogeneic relapse at 4apprx11 months after the transplantation. Only one patient has contiuing complete cytogeneic remisson up to now. Conclusion: The autogeneic prepherial blood stem cells transplantation

after Ph chromosome negative from chronic myeloid leukemia treated with STI 571 may be also relapse. What can we do for removing Ph chromosome postive cells meed future studing.

1/7/57
DIALOG(R)File 5:Biosis Previews(R)

0014814406 BIOSIS NO.: 200400182092
Reduced intensity stem cell cell transplantation (RIST) from unrelated umbilical cord blood (RI-UCBT) for the treatment of adult T-cell leukemia/lymphoma (ATL): A feasibility study with six patients.
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ABSTRACT: Background: Despite recent progress in cancer chemotherapy, the prognosis of both acute and lymphoma types of human T-cell lymphotropic virus type I (HTLV-I)-associated ATL remains poor. Reduced intensity stem cell cell transplantation (RIST) from unrelated umbilical cord blood (RI-UCBT) is a novel therapeutic strategy for patients with hematologic diseases who lack HLA-matched donors. We performed a feasibility study to test the role of RI-UCBT for the treatment of ATL. Patients and method: Between July 2002 and July 2002, 6 patients with ATL (median age, 58 y; range, 46-67: median body weight, 52kg; range 46-53: 3 acute, and 3 lymphoma type) underwent RI-UCBT. Chemotherapy preceding RI-UCBT had induced SD in 1, PR in 2 and PD in 3. Serological HLA matching was 5 of 6 in 2 patients, and 4 of 6 in the other 4 patients. Median number of infused all nucleated cells were 3.2X107/kg (range, 2.1-4.3). The condition regimen consisted of 25 mg/m2 fludarabine for 5 days, 80 mg/m2 melphalan for 1 day, and 4 Gy total body irradiation (TBI). Graft-versus-host disease (GVHD) prophylaxis was cyclosporine alone. All patients received G-CSF 300mug/m2 starting on day 1 until engraftment. Results: Complete donor T-cell chimerism was achieved progressively and rapidly, with cumulative incidences of 100% at day %28%. Three patients achieved primary neutrophil engraftment at a median time of 15 days. The remaining three patients died of complications (MRSA sepsis=1, encephalitis=1, and multiple organ failure=1) before neutrophil engraftment. Currently, 3 patients are alive and 2 patients developed acute GVHD (grade I and III). Regarding the clinical response, CR was observed in all patients. Estimated 6-months OS is 44% (95%CI: 16-100). Discussion: Although the number of patients is too small and the follow-up period is short, our results suggest that a strategy that incorporates RI-UCBT for ATL may be worth considering for further intense evaluation. At present, it has a considerable, GVL effect as well as severe transplant-related toxicities. The control of alloimmunity and management of transplant-related toxicities will be the focus of future investigation.

1/7/58
DIALOG(R)File 5:Biosis Previews(R)

0014814361 BIOSIS NO.: 200400182047
Analyzis of the toxicity and efficacy of donor lymphocyte infusions (DLI) after reduced intensity conditioning regimen allogeneic transplantations (RICT), given for either Mixed Chimerism and/or persistent disease.
AUTHOR: Michallet Anne-Sophie A S (Reprint); Nicolini Franck F (Reprint); Tremisi Jean-Paul J P; Dubois Valerie V; Hayette Sandrine S; Bourgeot Jean-Paul J P; Thomas Xavier X (Reprint); Gebuhrer Lucette L; Michallet Mauricette M (Reprint)
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ABSTRACT: To study after RICT, the DLI efficacy in terms of toxicity, chimerism conversion and disease response, we performed an analysis of 31 patients (19 M/12 F) with a median age of 46 y (19-60) receiving DLI either for disease progression (group1, n=23) or persistent Mixed Chimerism (MC) (group2, n=8). All conditioning regimens were with reduced intensity using fludarabine associated either to busulfan and ATG or 2 Grays TBI. The diagnosis before transplant were 5 NHL, 10 MM, 6 AML, 5 HD, 2 MDS, 1 CML in CP, 2 ALL. All patients received G-CSF mobilized PBSC from HLA identical sibling donors. GVHD prophylaxis was ciclosporine A (CsA) alone, CsA+MTX or CsA+Mycophenolate mofetil. We used 2 types of DLI regimens: BD (Bulk Dose) or ED (Escalating Dose). In group 1, 9 (39%) received BD and 14 (61%) ED. Three patients developed acute GVHD: 2 grade III (1 BD,1 ED), 1 grade IV after ED and 3 developed a de novo limited cGVHD after ED. Nine out of 23 (39%) achieved a disease response: 1 (4%) CR (NHL) who has developed a grade IV acute GVHD; 5 (22%) PR (3 AML, 2MM) and 3 (13%) remained in stable disease (1MM, 1NHL, 1MDS) with a median number of 2 DLI and a median interval between DLI of 1.5 months. Among these 9 DLI responders, 7 showed full donor chimerism and 2 a mixed chimerism (MC). The median follow-up in group 1 was 29 months, 19 (83%) died and 4 (%17%%) are alive (2MM, 1 NHL, 1 AML). The 3-year probability of survival for this group was 24% (95%CI (11-52)). In group 2, all patients were in CR after RICT with 4 stable and 4 progressive MC. Four BD (median dose: 0.01X108CD3+/kg) and 4 ED (0.01 to 3.62X108CD3+/kg) were given with a median delay of 3 months (3-9) between 2 DLI. Two patients developed an acute GVHD: 1 grade II after ED, 1 grade I after BD and 2 developed a de novo limited cGVHD after BD. Five patients (62.5%) established FDC after 3 BD and 2 ED with a median interval between 2 DLI of 2.3 months (1-29.5). At the last follow-up, 5/8 (62.5%) died (4 relapse and 1 infection); 3 (37.5%) are alive: 3MM (2CR (24months, 17months) and 1 PR (36months)). In conclusion, DLI allows substantial rates of chimerism conversion but these results point out the importance to perform earlier DLI when residual disease or chimerism markers are detected.

1/7/59
DIALOG(R)File 5:Biosis Previews(R)

0014814344 BIOSIS NO.: 200400182030
Reduced intensity conditioning with thiotepa, fludarabine and melphalan for allogeneic transplantation in multiple myeloma.
AUTHOR: Majolino Ignazio (Reprint); Arana Marcela Gabriel (Reprint); Riccardi Massimo (Reprint); Locasciulli Anna (Reprint); Bacigalupo Andrea ; Di Bartolomeo Paolo; Scime Rosanna; Olivieri Attilio; Narni Franco; De Fabritiis Paolo; Corradini Paolo
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ABSTRACT: In multiple myeloma (MM), autologous stem cell transplantation represents the treatment of choice for patients >60 y, but is not able to eradicate the disease. Allogeneic stem cell transplantation has been applied much less than autologous, due in part to a higher TRM, but it remains the only modality that may give a profound (molecular), long-lasting suppression of the neoplastic clone. With the intent of reducing the transplant death-rate, a low-intensity conditioning of fludarabine 3X30 mg/sqm, thiotepa 10 mg/sqm and melphalan 80 mg/sqm with allogeneic stem cell transplantation from HLA-identical sibling donors is under evaluation in a collaborative italian study. GVHD prophylaxis is based on low-dose-methotrexate plus cyclosporine, but the latter is rapidly tapered following transplantation to favor the emergence of an immune-mediated tumor suppression. DLIs are employed in those patients who remain mixed chimeras, are GVHD-free and still harbor detectable tumor following cyclosporin tapering. The study is supported by a molecular analysis of bone marrow cells to detect IgH gene mutation as minimal residual disease marker. Until now, 20 patients (41-64 y, median 53) have been allografted. Time from diagnosis to allograft was 3-66 mo. (median 8). Eleven had a progressed after single or double autograft. Seven were transplanted early in the course of their disease. As graft, they received 5.1X10-6/Kg (median) CD34+ cells (range 1.7-10.6), and 2.8X10-8/Kg CD3+ cells (range 0.4-4.2) from bone marrow or G-CSF-primed peripheral blood. Full engraftment occurred in all, with 14 days to recover >0.5X109/L granulocytes (range 10-%17%) and 12 days to recover >20X109/L platelets (range 4-21). Acute GVHD >grade I developed only in 5, but in none it was >grade II. Seven developed cGVHD. Sixteen patients were evaluable for transplant response as assessed at day +90. Ten were in CR (55%), including 4 patients who were already in CR at the time of allograft; 4 reached only a PR and 2 were refractory or progressed soon. There were no transplant related deaths. Until now there was a single relapse. The preliminary results of the present protocol show that the reduced-intensity conditioning with fludarabine, thiotepa and melphalan is well tolerated even in patients that have a long disease history or with previous autograft(s). It seems applicable also in elderly patients, or when co-morbidities would discourage the use of transplantation. Data of IgH-gene rearrangement are being produced and will possibly shed light on the significance of CR after this treatment. We actually offer this program to patients with an HLA-identical sibling donor at the time of induction, after 3-4 courses of VAD.

1/7/60
DIALOG(R)File 5:Biosis Previews(R)

0014814340 BIOSIS NO.: 200400182026
GVHD, mortality and control of leukemia in adult allogeneic BMT recipients with CML in CP1 given daily IV busulfan, fludarabine, and low-dose antithymocyte globulin (ATG): Comparison with historical experience using BuCy2 without ATG.
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ABSTRACT: A graft-vs-leukemia effect is relatively powerful after BMT for CML but may come at the cost of substantial morbidity and even mortality from GVHD. In previously reported studies pretransplant ATG appeared to reduce acute GVHD and early mortality of allogeneic SCT recipients. Intravenous busulfan (BU) may contribute to cytoreduction by allowing more predictable delivery than oral administration. From 1999-2003 a study group (S) of 19 patients (pts) with CML in CP1 received conditioning comprising fludarabine (FLU) 50mg/m2 on days -6 to -2 plus IV BU 3.2 mg/kg daily in a 3-hour infusion on days -5 to -2 inclusive (FLUBUP) followed by BMT from donors pretreated with G-CSF. Prophylaxis for GVHD included cyclosporine A (CSA), "short course" methotrexate (MTX) with folinic acid and Thymoglobulin (Sangstat) (ATG) 4.5 mg/kg in divided doses (0.5, 2 and 2mg) over 3 consecutive days finishing D-1 or D0. A historical control (HC) group (n=33) treated from 1988-1998 received BU 16mg/kg po and cyclophosphamide 120mg/kg as conditioning, conventional BMT and MTX/CSA as above for GVHD prevention. Acute GVHD grade II-IV occurred in 5+-5% of the S group, vs. 34+-9% of HC (p=0.03), and grade III-IV in none and %17%+-7% respectively (p=0.07). Incidence of chronic GVHD without donor lymphocyte infusion (DLI) at two years was 34+-11% (S) vs 72+-8% (HC) (p=0.02). There was a trend to less non-relapse mortality in S patients at zero vs 21+-7% at 3 years (p=0.06). With median followup of 24 months (range 1-51) for S and 141 months (range 64-185) for HC survival at 3 years was 100% vs 79+-7% respectively (p=0.06). However 3 deaths in the HC group occurred more than 9 years post-transplant Eight deaths in the HC patients were GVHD related the other 3 were due to another malignancy (pre-existing in one). Five S pts became PCR -ve within a year of BMT, 4 with de novo cGVHD, four are too early to evaluate (<10 mo). Eight S pts received escalating doses of DLI for hematologic relapse (1) or PCR positivity persisting beyond 10 mo (7). Three became PCR -ve with cGVHD and one without. One became PCR -ve after additional Gleevec, one is stable without further treatment, one has partial control of hematologic relapse with Gleevec, and one is too early to evaluate. Of pts not given DLI one with cGVHD and hematologic relapse did not tolerate Gleevec, one with persistent disease by PCR is stable on Gleevec. All evaluable HC pts became PCR -ve. Of 3 relapses beyond 5 years 2 were molecular, corrected by DLI, and one was cytogenetic currently being treated with Gleevec. In all 11 of 18 S pts beyond 6mo (61%) have developed cGVHD with or without DLI. A degree of clinical GVHD may be required for suppression of CML in many pts. However, the GVHD occurring de novo or after graded doses of DLI in the S group may be easier to control and possibly result in both better survival and quality of life in survivors. Nevertheless the majority of pts require further intervention after BMT with this protocol, and the role of DLI vs Gleevec for persistent/relapsed disease requires further study.

1/7/61
DIALOG(R)File 5:Biosis Previews(R)

0014814336 BIOSIS NO.: 200400182022
Allogeneic hematopoietic stem cell transplantation for treatment of acute lymphocytic leukemia.
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ABSTRACT: Objectives: To analyze the outcome of allogeneic stem cell transplantion (allo-SCT) for the treatment of ALL, and compare the effect

of preparative regimens, stem cell sources, and disease status before transplantation on the survival. Patients and methods: 88 patients were enrolled in this study. The median age was 30.0 y (range 4-47 y). 58 patients were transplanted in CR1, 13 in gtoreqCR2 and %17% in relapse. 79 patients were transplanted with HLA identical sibling grafts, from which 62 received BMT and %17% PBSCT (mobilized by glycosylated-G-CSF). For 9 patients transplanted with unrelated SCT, 6 received HLA-matched unrelated BMT and 3 cord blood transplantation. 44 patients were conditioned with BU/CY regimen and another 44 with CY/TBI regimen. GVHD prophylaxis consisted of CsA and short-term MTX for patients receiving sibling grafts. For unrelated SCT, MMF or methylprednisolone was also included in GVHD prophylactic regimens. The median follow-up was 30 months. Results: 5-year over all survival (OS) and leukemia-free survival (LFS) for all patients were 46.3% and 45.6% respectively. For patients transplanted in CR1, OS was 62.8% and LFS 62.1%. However, for patients transplanted in gtoreqCR2, OS and LFS were only 15.1% and 13.9%, respectively. Comparison of CY/TBI and BU/CY conditioning regimens shows that 5 year OS were 51.9% and 41.4% (P=0.152), and 5 year LFS were 49.9% and 44.1% (P=0.2188) respectively. Although there is no statistic significance between two conditioning regimens, CY/TBI regimen has a trend to increase the survival rate. BMT has the same effect on DFS compared with PBSCT, the 3 year LFS was 52.6% and 48.5% (P=0.546), respectively. Multivariate analysis showed that only two factors associated with good prognosis were that who transplanted in CR1 and continuous CR for more than 6 months. The conditioning regimens, age, sex, stem cell sources, GVHD prophylaxis had no significant effect on DFS. Conclusions: Allo-SCT can cure a significant proportion of ALL patients, especially for patients in CR1. BU/CY and CY/TBI conditioning regimens lead to similar outcomes, but the patients with CY/TBI had higher survival rate. These results suggest that patients with ALL should be transplanted in CR1 and use TBI-containing regimens, this will improve the outcome of allo-SCT.

1/7/62
DIALOG(R)File 5:Biosis Previews(R)

0014814313 BIOSIS NO.: 200400181999
Reduced intensity allogeneic stem cell transplant using CLAG-gleevec (imatinib mesylate) as preparative regimen for the treatment of acute myeloid leukemia relapse after first allogeneic stem cell transplant: A report of 3 cases.
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ABSTRACT: The outcome of relapsed AML post-allogeneic stem cell transplant (SCT) is poor. Optimal treatment is yet to be defined; options include salvage chemotherapy, immunosuppression withdrawal, DLI with or without chemotherapy, and second myeloablative allogeneic SCT. Potentially curative, the appeal of the latter is limited by considerable morbidity and mortality. Strategy, using second reduced intensity allogeneic SCT may be an alternative option. Purine analogue based regimens: FLAG (fludarabine, cytarabine and G-CSF) +/-Ida and CLAG (cladribine, cytarabine and G-CSF) were reported to be effective salvage regimens for relapsed leukemia. The purine-based regimens allow adequate cytoreduction as well as potent immunosuppression to allow allogeneic-SCT. Tyrosine kinase c-kit, the target for inhibition by imatinib mesylate, is present in 65-90% of AML cells. Imatinib mesylate had a synergistic effect with cytarabine and purines in-vitro AML cell lines. We report 3 cases of post allogeneic SCT AML relapse, treated with combination of CLAG chemotherapy regimen and imatinib mesylate as preparative regimen of a reduced intensity allogeneic SCT. Between October 2002 and February 2003, 3 patients with a history of AML (first case with secondary AML/MDS, second with primary refractory disease, and third with early relapse - 2 cases had multiple cytogenetic abnormalities) were diagnosed with post transplant relapse. Two patients had relapsed after myeloablative allogeneic SCT, and 1-after reduced intensity allogeneic SCT. Relapse occurred a mean of 240 days after the first transplant (range, 62-580). Patients were treated with cladribine, 5mg/m2 over 2 hours (days 2-6), cytarabine 2 gm/m2 over 4-hours starting 2 hours after cladribine (days 2-6), G-CSF 300mcg sc every day starting 24 hours before cladribine (Days 1-6), and imatinib mesylate 600 mg po daily (days 1-14). Patients received a second allogeneic SCT from the same donor at nadir of CLAG-Imatinib mesylate treatment. Only one patient received GVHD prophylaxis. All patients achieved engraftment and complete remission. The mean time to ANC >500 was 23 days (range, 20-27), and %28% days (range, 26-30) for platelets >50 k. One patient developed grade IV gut GVHD and was successfully treated. Side effects of CLAG-Imatinib mesylate regimen included febrile neutropenia (n=3), grade II skin rash and grade II edema (n=1). Mean leukemia-free survival was 152 days (range, 88-236). Overall survival equals the duration of follow-up, more than 220 days. Second reduced intensity SCT as a treatment option for the post-transplant relapse may warrant further investigation. Phase 1-2 study, evaluating CLAG-Imatinib mesylate in patients with relapsed or refractory AML, is currently being planned. A detailed and updated presentation of the three cases will be reported.

1/7/63
DIALOG(R)File 5:Biosis Previews(R)

0014814249 BIOSIS NO.: 200400181935
Successful management of invasive pulmonary aspergillosis (IPA) in two patients with high risk acute leukemia by combined antifungal treatment and reduced intensity conditioning (RIC) stem cell transplantation (SCT).
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LANGUAGE: English

ABSTRACT: Invasive pulmonary aspergillosis is a major cause of morbidity and mortality in immunocompromised patients undergoing allogeneic SCT. Combination of new antifungal agents might improve outcome in these patients. We transplanted two patients with high risk acute leukemia despite IPA using RIC and combined antifungal treatment. Patient 1: A 9-year-old girl developed IPA after second ALL relapse. Treatment with liposomal amphotericin B and caspofungin led to negativity of fungal markers and improvement of pulmonary CT findings. A mismatched unrelated SCT was performed after RIC under continuous antifungal therapy (liposomal amphotericin B 3-5 mg/kg/day for a total of 154 days, caspofungin 1-2 mg/kg/day for 181 days). Progression of IPA with destruction of 2 vertebrae 6 weeks after SCT was halted by tapering of immunosuppression, administration of G-CSF, higher antifungal doses and eventually triple combination with voriconazole (6-8 mg/kg/day for 94 days). Follow-up examinations 6 months after SCT showed resolution of the pulmonary and consolidation of the vertebral lesions. The patient is

alive in hematological remission without neurological sequelae 12 months after BMT. Patient 2: A %28%-year-old female with high risk AML developed IPA during prolonged neutropenia. Antifungal regimen at that time included caspofungin (70 mg/d on day 1, then 50 mg/d for 141 days) and liposomal amphotericin B (4-7 mg/kg/d for 39 days) followed by oral itraconazole (200 mg/d for 90 days). The patient underwent RIC-MUD-SCT. Since IPA progressed, antifungal therapy was changed to voriconazole monotherapy resulting in stabilization and, 7 weeks after stop of immunosuppression, in regression of pulmonary lesions. The patient has been in complete remission for 15 months. No dose limiting toxicity of liposomal amphotericin B or caspofungin occurred in either patient. Hallucinations probably related to voriconazole administration were observed in patient 1, but spontaneously improved on treatment continuation. Voriconazole and itraconazole were well tolerated by patient 2. These case reports clinically confirm superior activity of the new antifungal agents, particularly when administered in combination. In addition, faster immune reconstitution after RIC may improve prognosis in patients with high-risk leukemia and IPA.

1/7/64
DIALOG(R)File 5:Biosis Previews(R)

0014814247 BIOSIS NO.: 200400181933
Adoptive transfer of ex vivo costimulated autologous T-cells after autotransplantation for myeloma accelerates post-transplant T-cell recovery.
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ABSTRACT: Autologous T-cell responses against myeloma are defective partly due to a lack of costimulatory signals. Ex vivo co-stimulation of autologous T-cells using anti-CD3/anti-CD28-conjugated magnetic beads may restore T-cell recognition and responsiveness toward myeloma cells. 40 patients (pts) were enrolled in a clinical trial in which pts received infusions of ex-vivo co-stimulated autologous T-cells after autotransplantation. The mean age was 58 (range 43-72), 72% were male, 24% had IgA paraproteins, 12% had del 13 or complex karyotypes and the median beta2m level at diagnosis was 3.32 mg/L (range 1.09-73.7). All pts had steady state lymphocyte collections followed by cyclophosphamide (4.5 g/m2) and G-CSF for stem cell mobilization and melphalan (200 mg/m2 or 140 mg/m2 for pts gtoreq70) for high-dose therapy. T-cells were cultured for 12 days with anti-CD3/anti-CD28-immobilized immunomagnetic beads and IL-2 supplementation (100 units/ml). During a run-in phase, 12 pts received autologous T-cells post-transplant (apprxday +12) alone; afterwards, %28% pts participated in a 2X2 randomization in which they received T-cells "early" (day +12) or "late" (day +100) after transplant and also received 2 immunizations with the pneumococcal conjugate vaccine (PCV, Prevnar(R)) at days +30 and +90 or 3 immunizations (prior to T-cell collection, day +30, day +90) to test immune responses. 27 pts received one or more PCV immunizations and there were no grade 3/4 adverse events. Anti-pneumococcal antibody and T-cell response assays are in progress for those pts who have completed the study. 33 pts received a mean of 8.11X109 costimulated cells (range 1.6-11) and all infusions have been well tolerated except for chills and rigors. There have been no delayed adverse effects except for grade 1-2 facial/upper body rashes in 6 pts which were possibly or probably related to the T-cell infusions (median 13 days after T-cells) and 1 episode of grade 2 conjunctivitis. At the time of T-cell harvesting, the mean % of CD3+ cells in culture was 94.2% and the mean T-cell doubling level during the 12 day culture was 5.2. Among the randomized pts, at day +42 post-transplant (apprx30 days after T-cell infusion for the "early" groups), the mean CD4/CD3 count was 679/mul (95% CI, 347-1012) for the "early" T-cell recipients vs 278/mul (95% CI, 59-497) for the "late" T-cell recipients (T-cells not yet infused) (P=0.03). The mean CD8/CD3 counts were 1826/mul (95% CI, 1275-2376) and 1105/mul (95% CI, 404-1806) for the "early" and "late" T-cell recipients respectively at day +42 (P=0.07). There were 2 treatment-related deaths on the trial: one patient died from neutropenic sepsis during mobilization; one patient with renal amyloidosis and myeloma died from sepsis and renal failure. Neither patient received T-cell infusions. 32 pts are evaluable for clinical responses, while 8 are too early to evaluate. There were 6 CRs, 15 VGPRs (gtoreq90% reduction in paraprotein levels), 10 PRs (50-90% reductions), and 1 patient had no response. 15 pts had progressive disease at a median of 8 months after transplant. In summary, infusions of ex-vivo expanded autologous T-cells are feasible and well-tolerated post-transplant and may be associated with accelerated recovery of T-cell counts.

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DIALOG(R)File 5:Biosis Previews(R)

0014814239 BIOSIS NO.: 200400181925
Topotecan (T) and melphalan (M) With autologous stem cell transplantation (ASCT) is a safe, tolerable and effective regimen for patients with multiple myeloma (MM).
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ABSTRACT: T is a topoisomerase I inhibitor. Its primary and most common toxicity is reversible myelosuppression. This makes it a potentially useful drug for inclusion in high dose regimens accompanied by stem cell rescue. Single agent activity has been reported in both hematologic and solid malignancies. MM is an incurable malignancy with conventional chemotherapy, A number of randomized studies have demonstrated the benefit of high dose chemotherapy with ASCT however relapse is inevitable. Most patients have received either high dose M alone or in combination with TBI. T has been shown to have activity in MM and NHL as a single agent or in combination. To evaluate the safety and tolerability of an escalating dose of T in combination with M, we have performed a phaseI/II study involving 20 MM (gtoreqDurie-Salmon Stage 2) patients and 3 NHL patients. Patients received M 140mg/m2 in combination with 1 of 3 doses of T. (Level 1=3.3mg/m2; level 2=6.7mg/m2; level 3=10mg/m2). M was administered over 30 minutes on days -6 and -5. T was administered over 30 minutes on days -4, -3 and -2. G-CSF was administered from day +5 until neutrophil engraftment. Rapid escalation to dose level 3 was achieved using the continuous reassessment method (CRM). Dose limiting toxicity (DLT) was defined as any grade 4 non-hematologic toxicity. Following the CRM, 2 patients received dose level 1 with no DLT. The next

3 patients received dose level 2 with no DLT. The 6th patient received dose level 3 and experienced grade 4 mucositis. The subsequent 3 patients received dose level 2 with no DLT but grade 3 mucositis occurred in all 3 patients. 14 additional patients received dose level 3 and no DLT was observed. 5 patients developed grade 3 mucositis. Mucositis was grade 2 in 3 patients and grade 1 in 2 patients. All patients developed predictable grade 4 myelosuppression. In an attempt to reduce regimen related mucositis we administered propantheline to 6 patients treated at dose level 3. Propantheline is an anticholinergic agent reported to provide oral mucosal protection during high dose chemotherapy. Of the 15 patients receiving T dose level 3, 6 received propantheline and 8 did not. Of the 8 patients not receiving propantheline, 7 developed mucositis (87.5%). In 5 patients, this was grade 3, in 2 it was grade 2 and in one case, grade 1. Of the 6 patients receiving propantheline, only 3 developed mucositis (50%). All patients engrafted without delay (mean and median days to ANC >500=10 days; mean and median days to platelet >20=11). No regimen related deaths occurred. Regarding efficacy, of %17% MM patients with a PR from their most recent therapy, 4 (23.5%) had a CR following HDT/ASCT. Of 2 patients with SD in response to their most recent therapy, 1 achieved a PR and 1 had SD post-transplant. 1 patient with PD prior to transplant achieved disease stability. Of the NHL patients, 1 with PD prior to transplant achieved a CR. The remaining 2 patients had persistent SD. Responses for the entire patient cohort related to the T dose level are given. We conclude that T 10mg/m2 combined with M 140mg/m2 is a safe and tolerable regimen when used with ASCT and has a similar CR rate as is reported for high dose M alone in MM. We also conclude that propantheline administered orally during chemotherapy may reduce regimen related mucositis.

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DIALOG(R)File 5:Biosis Previews(R)

0014814185 BIOSIS NO.: 200400181871
A method for large scale enrichment of human gammadelta T cells suitable for cellular immunotherapy.
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ABSTRACT: gammadelta T cells are a small proportion of human peripheral lymphocytes and account for less than 10% of the peripheral T cell population. In contrast, their presence is much higher in certain epithelia-rich tissues such as gut, skin or reproductive tract. gammadelta T cells have shown to exert potent antitumor and antimicrobial activity both in vitro and in vivo. In addition, they do not seem to be alloreactive, thus making them attractive candidates for cell-based immunotherapy. Therefore we evaluated the efficacy and feasibility of a large scale enrichment of human gammadelta T cells. In 5 experiments we processed cells derived by leukapheresis from healthy, G-CSF mobilized volunteers. Cells were incubated with an anti-TCR gammadelta-hapten antibody and consecutively with an anti-hapten antibody conjugated to magnetic beads (Miltenyi, Bergisch-Gladbach, Germany). gammadelta T cells were then collected by positive enrichment using the CliniMACS device (Miltenyi). Results: The mean number of processed mononuclear cells was 10.6X109 (range 6-%17%). Pre enrichment, the percentage of pan-gammadelta positive PMNC in the leukapheresis product was 2.1% (range 1.6-6.4). Mean yielded purity of isolated gammadelta T cells was 90.2% (range 77-96.6%) with a recovery rate of 61.4% (range 38.7-90.6). Cell viability was always greater than 80%. In comparison to peripheral lymphocytes from immobilized individuals, the isolated gammadelta cells showed a much higher expression of CD8 (up to 49%), CD28 (up to 67%), and CD11b/CD18 (MAC-1, up to 74%). One donor expressed almost exclusively a Vgamma9delta1 T cell receptor (TCR) subtype, one a 25% Vgamma9delta2 and 75% Vgamma9Vdelta1 phenotype, another 50% Vgamma9delta1 and 50% Vgamma9delta1. Two donors expressed the Vgamma9delta2 TCR only. Cytotoxic capacity of freshly isolated gammadelta T cells and after stimulation with 200IU/ml interleukin-2 for 72 hrs. were shown in a conventional cytotoxicity assay (EuropiumTDA release, PerkinElmer Wallac, Norton, OH) against several tumor cell lines and in a mouse model of disseminated neuroblastoma as described elsewhere. In conclusion, we describe a safe and for clinical applications suitable method for large-scale enrichment of human gammadelta T cells by immunomagnetic positive selection.

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DIALOG(R)File 5:Biosis Previews(R)

0014814149 BIOSIS NO.: 200400181835
Comparison of myeloid (MDC) and plasmacytoid dendritic cells (PDC) content between two stem cell products: Cord blood and G-CSF mobilized peripheral blood aphaeresis from healthy donors.
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ABSTRACT: DC is thought to be the key cells in the initiation and modulation of immune responses. Myeloid and lymphoid DC has already been identified in adult human peripheral blood and cord blood. For immunotherapy protocols, large numbers of DC are currently needed, hence, DC numbers in the different sources of hematopoyetic cells are important to be defined. Aim: to determinate DC content on Cord blood (CB) and G-CSF mobilized peripheral blood aphaeresis (PBA) by quantification of the different subsets described by flow cytometry. MM: Umbilical cord blood samples were obtained from normal full term deliveries and collected under Barcelona Cord blood Bank SOPs. Samples from G-CSF mobilized peripheral blood (of first aphaeresis product) were taken from healthy donors of patients undergoing BMT (mean age: 40+-%17%). DC population was defined as DR+, LIN/34 dim/-. MDC (DC1) was defined as 11c+, 123 dim/-; PDC (DC2) was defined as 123 high+, 11c-; less differentiated DC (ID DC) was defined as 11c-, CD123 dim+. Results: The mean total nucleated cell (TNC) content was 11.7+-3.6 and 306+-152 (106/ml) in a mean volume of 123.3+-50 and 231.1+-63.4 for CB and PBA respectively. Mean MNC content was 47.5+-6.4% and 80.7+-15.2% respectively. The mean DC content was 0.04+-0.06% and 0.3+-0.1% of TNC in CB and aphaeresis respectively. These data result in an overall content of 0.7+-1.0X106 and 229+-136X106 respectively. Conclusion: PBA have significantly more DCs counts than cord blood counterpart (up to 322 times). Moreover, intersample variability in CB was remarkably higher than in PBA. Plasmacytoid DCs are the predominant circulating DC subtype in both sources (51 and 63% respectively). Despite the fact that absolute numbers varies between these two sources, the three populations are similarly represented in each inoculum. ID DC and plasmacytoid failed to show age dependency decrease in the analyzed population, however population is small and further studies are necessary to verify these findings.

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DIALOG(R)File 5:Biosis Previews(R)

0014814146 BIOSIS NO.: 200400181832
Peripheral blood stem cell (PBSC) collection in high risk patients affected with primary systemic amyloidosis. A single center experience on 31 patients.
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ABSTRACT: Autologous blood stem cell transplantation (aSCT) is a new therapeutic chance in selected patients affected with primary systemic amyloidosis. High dose Melphalan followed by infusion of peripheral blood collected stem cells can improve survival of these patients. It's documented that G-CSF mobilization +/- associated with chemotherapy and collection by cell separator are weighted with an higher rate of morbidity and mortality (15%) if compared with other pathologies. In fact, cardiac involvement, hypoalbuminemia, dysautonomic manifestations with hemodinamic instability, noticeably increase the risks related to mobilization and collection of stem cells. 31 pts, 20 M and 11 F, median age 51.8 yrs (%28%-68), affected with primary systemic amyloidosis, underwent peripheral blood stem cell collection (PBSCc) in our Center. 27/31 (87%) pts presented cardiac, 26/31 (83%) renal, 5/31(16.1%) peripheral nervous system, 4/31(12.9%) liver and 2/31 (6.4%) cutaneous involvement. 25 pts were mobilized with G-CSF alone (10 m g/Kg) and 6 with CTX (3 gr/m2) plus G-CSF (10m g/Kg). Our collection strategy consisted in processing 3.5 blood volumes using the Spectra Cobe (version 6.0) cell separator device. To minimize the occurrence of hypotensive episodes and hemodinamic instability we decided to infuse 100 ml of human albumin (20%): 50 ml immediately at the beginning of the collection and the remaining 50 ml within the 1st hour of the procedure. All pts were continously monitored for blood pressure and heart rate during the entire collection procedure. A minimum dose of 4X106/Kg CD34+ cells was requested to support at least 1 aSCT. At time of collection pts mobilized with G-CSF alone had a median WBC count of 50.5X106/ml (27-77) with a median CD 34+ cells count/m L of 48.4 (21-99.6). On the contrary, chemotherapy mobilized pts had a median WBC count of 12.8X106/ml (5.9-22) with a median CD 34+ cells count/m L of 59.9 (26-111). 3 pts failed mobilization with G-CSF alone and were turned to the chemotherapy mobilizing regimen. The median number of collections/pts either with G-CSF or CTX was 1.8 (1-3). The median number of CD34+ cells collected in pts mobilized with G-CSF alone was 8.3X106/Kg (1.35-21.3) and in pts mobilized with CTX+ G-CSF was 8.5X106/Kg (5.5-14.9). 29/31 pts (93.5%) were able to reach the requested minimum CD34+ cell target dose (4X106/Kg) dose; on the contrary, 2/31 pts (6.4%) failed. During the collection in 12 pts (38.7%) an asymptomatic hypotensive episode and in 1 pts (3%) a symptomatic episode (nausea and vomiting) were registered. Moreover 2/31 pts (6.4%) had a life-treathening hypotensive episode. No procedure related deaths occurred. PBSCc procedure in pts affected with primary systemic amyloidosis confirms to be feasible and relatively safe. A close monitoring of CD34+ cells mobilization and a careful management of the pts during the entire collection permit to reach the CD34+ transplant cell dose in a high percentage of pts, reducing the collection related risks and offering, at the same time, an important therapeutic chance.

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DIALOG(R)File 5:Biosis Previews(R)

0014814140 BIOSIS NO.: 200400181826
Peripheral blood stem cell mobilization with ESHAP and G-CSF in patients with relapsed and/or refractory Hodgkin's disease and non-Hodgkin's Lymphoma.
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ABSTRACT: Myeloablative chemotherapy with autologous peripheral blood stem cell support has an increasingly important role in relapsed and/or refractory Hodgkin's disease (HD) and non-Hodgkin's Lymphoma (NHL). Most of the centers prefer peripheral blood as a stem cell source because its easy to collect, contamination is lower than bone marrow and engraftment occurs rapidly. Herein we investigated the efficiency of ESHAP (Etoposide, 40 mg/m2/d, iv, 1-4 days, methylprednisolone 500 mg/d iv, 1-4 days, cisplatin 25 mg/m2/d iv, 1-4 days, cytarabine, 2000 mg/m2, iv, fifth day) regimen with G-CSF in stem cell mobilization which has been given as salvage therapy in HD and NHL. Eighteen patients with relapsed and/or refractory HD (n=8) and NHL (n=10) were included into the study. G-CSF (10 mug/kg/day, SC, (filgrastrim)) was started at the 6th day of ESHAP chemotherapy and continued until apheresis. After the elevation of peripheral blood CD34 positive (+) cell count over 20/mul apheresis was started. The minimum target dose of harvested CD34+ cell was 2.5X106/kg body weight. Peripheral blood CD34+ cell count increased over 20/mul in %17% patients and all these patients were processed to apheresis median 14th (range 12-24 days) day of ESHAP chemotherapy. The platelet count of one patient never increased the safety levels for apheresis due to platelet refractoriness and the other patient couldn't achieve the target number of CD34+ cell in two apheresis process. The median number of apheresis was 2 (range 1-3). The median CD34+ cell count per apheresis was 7.0X106/kg (range 0.7-32.5X106/kg). There were no difference between HD and NHL patients in median day of apheresis, median CD 34+ cell count per apheresis and the number of apheresis. The only complication of ESHAP chemotherapy was febrile neutropenic attack. As a result according to our study ESHAP chemotherapy not only a good salvage regimen but also a good stem cell mobilization protocol with G-CSF.

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DIALOG(R)File 5:Biosis Previews(R)

0014814008 BIOSIS NO.: 200400181694
Peripheral blood stem cell collection after CAD plus G-CSF in Multiple Myeloma: No influence of previous thalidomide administration.
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ABSTRACT: OBJECTIVES: Thalidomide (Thal) induced remission in 40% of refractory Multiple Myeloma (MM) patients (pts.). Munshi et al. (Blood 1999, Abstract 2577) described a dampening of peripheral blood stem cell collection (PBSC) in pts. treated with Thal. In a joint study of GMMG/HOVON group induction therapy with Thal, doxorubicin and dexamethasone (TAD) is investigated in comparison with vincristine, doxorubicin and dexamethasone (VAD). METHODS: Altogether, data of 60 pts. treated in our clinic were analyzed in terms of PBSC. 30 pts. were randomized up-front to receives cycles of TAD (Thal 400mg/d orally; doxorubicin 9mg/m2/d, 4 inf. a 30 min., day 1-4; dexamethasone 480mg total dose or.). 30 pts. received VAD (vincristine 0.4mg/d and doxorubicin 9mg/m2/d, 4 inf. a 30 min., day 1-4.; dexamethasone 480mg total dose or.) followed by mobilisation with CAD (cyclophosphamide 1g/m2/d, inf. a 1h, day 1; doxorubicin 15mg/m2/d, 4 short inf., day 1-4; dexamethasone 160mg total dose or.) and granulocyte colony-stimulating factor (G-CSF) (Neupogen 600mug/d s.c. or Granocyte 526mug/d s.c., day 5 after the end of chemotherapy until PBSC). Thal was stopped two weeks before CAD. Low dose heparin administration was performed to prevent deep vein thrombosis (DVT) in TAD group. RESULTS: A median of 14 days after first day of CAD until PBSC was found in both TAD (range 11-%17% days) and VAD (range 9-20 days) (p=0.12). In the first leucapheresis a median total PBSC yield of 10X106/kg CD 34+ cells in the TAD/CAD (range 0.3-34X106 CD34+ cells) and 9.8X106/kg CD 34+ cells in the VAD/CAD (range 3-30X106 CD34+cells) group could be harvested (p=0.6). There was also no difference between both groups in terms of best leucapheresis (p=0.7) defined by the highest number of CD34+ cells/kg BW. CONCLUSIONS: No difference was found in peripheral blood stem cell collection after TAD versus VAD in first as well as best leucapheresis.

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DIALOG(R)File 5:Biosis Previews(R)

0014813836 BIOSIS NO.: 200400181522
Hematologic responses after myeloablative therapy with i.v. treosulfan and autologous peripheral blood progenitor cell transplantation (PBPCT) in patients with myelofibrosis with myeloid metaplasia: One year follow-up results.
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ABSTRACT: Myelofibrosis with myeloid metaplasia is a chronic myeloproliferative disorder. The only curative therapy to date is myeloablation followed by allogeneic transplantation. This approach, however, is associated with a high morbidity and mortality. Autologous transplantation after myeloablation with high-dose oral busulfan provides a palliative approach which can lead to a long-term relief of symptoms and is associated with acceptable morbidity and mortality (Anderson JE et al. 2001, Blood 98: 586). However, busulfan pharmacokinetics after oral administration can vary between patients and increased toxicity is encountered in some. On the other hand treosulfan, a bi-functional alkylating drug, can be administered safely i.v. with reliable pharmacokinetics up to the myeloablative dose range. In the study presented here, patients were stimulated with G-CSF 16 mg/kg daily for 4 days and subsequent leukapheresis of a minimum of 5X106 CD34+ cells/kg was performed. Myeloablation consisted of treosulfan infusions of 14 g/m2 for three consecutive days (total dose 42 g/m2) and subsequent autologous PBPCT. To date we have transplanted 3 patients, all female. Two patients (1, 3) had symptomatic splenomegaly and severe anemia. Patient 2 had symptomatic splenomegaly and thrombocytopenia (<100/nl). The WB nadir after treosulfan therapy was 0.06/nl (1), 0.%28%/nl (2) and 0.09/nl (3). The time to reconstitution of leucocytes >1/nl post transplantation was %28% days (1, 2) and 38 days (3) and the time for reconstitution of thrombocytes >50/nl was 36 (1), 22 (2) and 33 (3) days. The prolonged reconstitution period may have been due to the myelofibrosis and has also been observed after busulfan conditioning and PBPCT by others. There were no fever or other severe toxicity. Patients did not require total parenteral nutrition. The patients are now day 515, day 461 and day 434 post transplantation. The first patient (1), who required erythrocyte transfusions twice weekly pretransplant received her last erythrocyte transfusion on day 56; her Hb-value is 11.2 g/dl at last follow-up. The second patient (2) recovered to platelet counts higher than pre-transplantation (58/nl) at 3 months.(143/nl) and had 90/nl at last follow-up. Pat. 3 showed a marked reduction of the maximum spleen size and a rise in Hb from 9 g/dl to 11.8 g/dl. We therefore conclude that myeloablation with treosulfan and autologous PBPCT is a safe and efficient treatment for patients with myelofibrosis.

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DIALOG(R)File 5:Biosis Previews(R)

0014813565 BIOSIS NO.: 200400181251
Non-myeloablative conditioning with total lymphoid irradiation (TLI) and anti-thymocyte globulin (ATG) for allogeneic hematopoietic cell transplantation (HCT) results in high levels of regulatory natural killer T cells and low incidences of acute GVHD and tumor relapse.
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ABSTRACT: Natural killer T (NK T) cells constitute a unique class of immune regulatory cells that express an invariant TCR alpha chain, recognize CD1 instead of MHC antigen presenting molecules, elaborate high levels of IFN-gamma, IL-4 and IL-10, kill tumor cells, and suppress conventional T cell alloreactivity. Preclinical studies in rodents have shown that non-myeloablative conditioning with TLI combined with depletive anti-T cell antibodies protects against lethal acute GVHD (aGVHD) after MHC mismatched HCT by skewing residual host T cell subsets to favor suppressive regulatory NK T cells. We have adapted the murine protocol to a clinical regimen of TLI (10 doses of 80 cGy/dose) and rabbit ATG (5 doses of 1.5 mg/kg/dose) with post-grafting immunosuppression of mycophenylate mofetil (MMF) and cyclosporin (CSP) to determine if the regimen protects against aGVHD also in humans. Seventeen patients with extensively pretreated hemato-lymphoid malignancies received related (9) or unrelated (8) HLA matched G-CSF mobilized HCT. Eight of the patients

had relapsed after prior autologous transplants. 11 were in a partial remission (PR) at the time of allogeneic transplant, 2 had progressive disease (PD) and 4 were in complete remission (CR). Following transplantation all patients had complete and sustained multi-lineage donor chimerism except the 2 patients with PD who displayed transient high levels of donor chimerism. The median follow-up (F/U) for all patients is 308 days, with 8 patients having F/U beyond 1 year. Sixteen of %17% patients had grade 0 aGVHD and 1 patient had grade III aGVHD that responded to steroid therapy. Of the 11 patients transplanted in PR, 10 achieved a CR and have not relapsed, and 1 died from TTP before evaluation. The 4 patients transplanted in CR continue to be in CR yet the 2 patients transplanted with PD did not clear their tumor. Opportunistic infection was observed in one patient with CMV disease of the gastrointestinal tract that resolved with DHPG therapy. Four patients have died from PD (1), indwelling line sepsis (1), TTP (1) and suicide (1). Monitoring of T cell subsets before the conditioning regimen and after transplantation revealed a discrete subset of CD8+NK T cells (CD161hiValpha24+Vbeta11+) among peripheral blood mononuclear cells (PBMC) starting 2 weeks after transplantation in six of six patients tested which persisted for at least 6 to 12 months. The subset accounted for a mean of 8% of CD8+ T cells and the percentage of all CD8 T cells was several folds higher than CD4 T cells. The discrete subset was observed in none of the six patients before TLI/ATG conditioning. Activation of PBMC with PMA and ionomycin showed that CD161+/CD3+ cells expressed high levels of intracellular IL-4 and IL-10 with little IFN-gamma. Monitoring of control transplant patients conditioned with TBI (200cGy) and Fludarabine showed that none of six had a discrete subset of CD8+ NK T cells before conditioning and only one of six developed the subset after transplantation. In conclusion, conditioning with TLI/ATG resulted in sustained donor chimerism, a markedly reduced incidence of aGVHD without tumor relapse and a low incidence of infections. We show evidence that as in the pre-clinical model the low incidence of aGVHD is associated with increased levels of NK T cells.

1/7/73
DIALOG(R)File 5:Biosis Previews(R)

0014813529 BIOSIS NO.: 200400181215
Taxol plus topotecan plus rituximab (TTR) with G-CSF support: An effective salvage program for the treatment of patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (NHL) who failed CHOP-like and platinum-based therapy.
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ABSTRACT: Aproximately 55% of patients with newly diagnosed aggressive B-cell NHL will be cured of disease with current induction therapy. For those who do not respond to front-line therapy (primary refractory) or relapse from remission, platinum-based salvage therapy and stem cell transplantation may offer a second chance for a cure in subset of these patients. However, treatment of patients who fail platinum-based therapies, or those who cannot tolerate such programs remains challenging. Furthermore, the contribution of rituximab to salvage programs in these patients remains unknown. We have recently reported our experience using Taxol+Topotecan in patients with relapsed aggressive NHL. Using similar eligibility criteria, we designed a follow-up phase II study combining the same doses of Taxol (200 mg/m2 IV day 1 over 3 hours) and Topotecan (1 mg/m2 IV QD day 1-5), but combined with rituximab (375 mg/m2) which was given one day prior to starting each course of Taxol+Topotecan. All patients received prophylactic G-CSF support and courses were repeated every 3 weeks. Responding patients received a maximum of 6 courses or were offered stem cell transplantation after a minimum of 2 courses. Seventy-one patients are evaluable for treatment response and toxicity. Median age was 55 years (Range 18-78). Patients had relapsed or refractory diffuse large B-cell NHL, follicular large cell or transformed B-cell NHL. The median number of prior treatment regimen was 1 (range 1-2), and 32 (45%) patients had primary refractory disease (failed to achieve CR after first induction therapy). All patients were previously treated with CHOP, or CHOP-like induction regimens, and 20 patients (%28%%) received prior Ara-C/platinum containing regimen. Forty-one (57%) patients had an elevated pretreatment LDH. Patients received a median of 3 courses (range, 1-6). Response to TTR therapy according to disease sensitivity is compared to our previous experience with Taxol+Topotecan in similar patient population. Thus, the addition of rituximab to Taxol+Topotecan not only improved the overall response rate, but also the CR rate. Furthermore, TTR induced a 45% response rate in patients who failed prior platinum containing regimens. Patients received a total of 269 cycles of therapy. Twenty-three patients required dose reduction of at least one dose due to toxicity. Treatment was reasonably well tolerated and most non-hematologic toxicities were of grade I and II. Grade IV neutropenic infection was observed in 3 patients. Neutrophil count of less than 500/ml was observed after 31% of the cycles, and platelet count of less than 10,000/ml was observed after 5% of the cycles. We conclude that TTR is an effective new salvage therapy for patients with relapsed/refractory aggressive B cell NHL who failed prior CHOP-like or platinum-containing regimens.

1/7/74
DIALOG(R)File 5:Biosis Previews(R)

0014813210 BIOSIS NO.: 200400180896
A unique role for retinoic acid receptor gamma (RARgamma) in the regulation of granulopoiesis.
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LANGUAGE: English
ABSTRACT: The retinoic acid receptors (RARs) have known roles in inducing the differentiation of both leukemic and normal granulocytes, with their natural ligand, all-trans retinoic acid (ATRA). used as a curative therapy for patients with acute promyelocytic leukemia. However, despite the perceived prominent role of RARalpha in granulopoiesis, we, and others have reported that RARalpha knockout (KO) mice have normal granulopoiesis in vivo. In marked contrast, we recently observed that RARgammaKO mice have hematopoietic disorders in multiple lineages, including simeq300% increase in peripheral blood (PB) granulocytes. We therefore undertook studies to further explore the nature of the granulocytic defect in adult RARgammaKO mice. Despite being 20% smaller than their wildtype (WT) littermates, the bone marrow (BM) leukocyte cellularity of RARgammaKO mice was significantly increased compared to that of WT littermates: WT=%28%.50+-2.79, heterozygotes (HT)=32.34+-1.91, KO=34.41+-1.81X106 cells/femur (n>5, p<0.05 WT vs. KO). This was due to a striking increase in BM granulocytes: WT=13.08+-1.62, HT=13.84+-0.99,

KO=22.76+-3.17X106 granulocytes/femur (n>5, p<0.05 WT vs. KO). In keeping with the elevated granulocytes observed in the PB and BM of these mice, there were increased granulocytes in the spleens of RARgammaKO mice: WT=0.45+-0.06, HT=0.46+-0.15, KO=3.59+-1.28X107 granulocytes/spleen (n>5, p<0.05 WT vs. KO). To investigate further the nature of the increase in granulocytes in RARgamma KO mice, we examined the production of single-factor responsive day 7 colony-forming cells (CFCs) and day 3 granulocyte cluster-forming cell (CFCs) per 5X104 RARgamma WT, HT and KO BM cells. We observed a significant increase in all of these progenitors from RARgammaKO BM. Surprisingly, there was also a significant decrease in the numbers of all of these progenitors from RARgamma HT BM. There were no differences in the apoptotic properties of BM progenitors, as measured by cytokine withdrawal assays, or mature spleen-derived granulocytes, as measured by annexin V/7AAD staining, from any of the mice, hence these defects in mature granulocyte progenitors are not likely due to altered survival of these cells, but rather may result from altered differentiation of myeloid precursors in the RARgammaHT and KO mice. We did not detect any differences in RARalpha or RARbeta transcript expression in granulocyte populations obtained from RARgamma mutant mice, hence these defects are not likely due to compensatory mechanisms within the RAR gene family. We are therefore currently undertaking an integrated three-way microarray and bioinformatics approach using RARgamma WT, HT and KO granulocytes to identify key target genes that are involved in the regulation of granulopoiesis by RARgamma and this data will be presented. Interestingly, no phenotype in granulopoiesis was observed in RARalpha mutants, contrasting with the distinct phenotype of the RARgamma mutant mice. These data therefore reveal a novel, previously unrecognised, non-redundant role of RARgamma in the regulation of granulopoiesis.

1/7/75
DIALOG(R)File 5:Biosis Previews(R)

0014801939 BIOSIS NO.: 200400172696
Retroviral vector integration into the genome of rhesus macaque long-term repopulating cells appears to be non-random, and recurrent integration loci include MDS1 and HIPK2.
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ABSTRACT: Replication defective murine retroviruses are widely used as gene transfer vectors, but the development of leukemia after hematopoietic stem cell (HSC) gene therapy for immunodeficiency has refocused attention on the capability of these vectors to cause insertional mutagenesis. Recent large-scale analyses of retroviral integration sites (RIS) in human cell lines have found that non-replicative HIV-1 and MLV-derived vectors favor active genes and transcription start regions respectively. However, large-scale analysis of RIS in a relevant pre-clinical situation is essential to better evaluate the clinical safety of HSC retrovirus-based gene therapy. Here we report the mapping of 200 RIS in a long-term model of autologous retrovirally-transduced HSC transplantation in the non-human primate (Macaca mulatta). Granulocytes, T and B lymphocytes and mononuclear cells from five rhesus macaques (number of insertion sites per animal=70, 70, 29, 25 and 6), transplanted with G-CSF+SCF mobilized CD34+ peripheral blood stem cells, have been analyzed between one and two years following transplantation. After DNA extraction and inverse PCR (n=99) or linear-amplification mediated PCR (n=101), genomic regions adjacent to RIS have been cloned. A sequence was considered as a genuine RIS only if it contained the LTR sequence (inverse PCR) or both the LTR sequence and the linker sequence (LAM-PCR), matched to a genomic location starting at the end of the LTR, showed at least 90% identity to the April 2003 assembly of the Human Genome, and yielded a unique best hit in the BLAT ranking. Out of the 200 RIS analyzed, 80 (40%) landed between the transcriptional start and stop codons of a RefSeq gene, roughly two times more frequently than computer-simulated integrations (Wu X. et al., Nature, 300:1749). Analysis of the targeted genes reveals strong evidence for non-random insertion: two monkeys have independent RIS in the gene coding for the homeodomain interacting protein kinase 2 (HIPK2), a nuclear protein kinase that directly phosphorylates p53, and three others monkeys have RIS in the myelodysplasia syndrome 1 gene (MDS1). MDS1 is involved in recurrent translocations in patients with myeloid leukemias, with a second gene, ecotropic integration 1 (EVI1), expressed as fusion genes with portions of either AML1 or TEL; the murine homolog of EVII is a well-known target of insertional mutagenesis by replication-competent and replication-defective retroviruses. It is also noteworthy that out of the remaining 75 genes with RIS, two others are known to be involved in leukemic translocation: hepatic leukemia factor (HLF) involved in t(%17%;19) translocation in B-ALL, and MLL septin-like fusion (MSF), involved in t(11;%17%) AML. Of note, all animals have now been followed for 30 to 64 months following transplantation, and none has developed progression to an oligoclonal or monoclonal pattern of hematopoiesis, and all remain hematologically normal. These results indicate that retroviral integration in HSC-targeted gene therapy is a non-random process that targets specific loci: this is, to our knowledge, the first report of identification of common integration sites after gene marking experiments in a relevant pre-clinical model. Systematic analysis of RIS after HSC gene transfer in the non-human primate will provide extensive pre-clinical data necessary for evaluating the integration characteristics of clinical vectors, and offers also a powerful means for identifying genes involved in the biology of HSC.

1/7/76
DIALOG(R)File 5:Biosis Previews(R)

0014801883 BIOSIS NO.: 200400172640
Use of glycosylated recombinant human G-CSF during and/or after induction chemotherapy in elderly patients with acute myeloid leukemia: Final results of AML-13, a randomized phase III study of the EORTC and GIMEMA leukemia groups.
AUTHOR: Amadori Sergio (Reprint); Suciu S (Reprint); Jehn U (Reprint); Thomas X (Reprint); Marie J-P (Reprint); Muus P (Reprint); Varet B (Reprint); Berneman Z (Reprint); Fillet G (Reprint); Denzlinger C (Reprint); Willemze R (Reprint); Nobile F (Reprint); Leoni P (Reprint); Leone G (Reprint); Fabris P (Reprint); Ricciuti F (Reprint); Vignetti M (Reprint); Beeldens F (Reprint); Mandelli F (Reprint); de Witte T (Reprint)
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ABSTRACT: Aim of this prospective, multicenter trial was to investigate, using a 2X2 factorial design, whether G-CSF administered during and/or after induction chemotherapy would affect complete remission (CR) rate, infection rate, neutrophil recovery, or survival in patients aged 61-80 yrs with previously untreated AML. Lenograstim (Granocyte(R), Chugay-Aventis) was given daily at 150 mug/m2 by 30-min iv infusion in conjunction with induction chemotherapy consisting of 1-2 courses of the MICE regimen (mitoxantrone, etoposide, cytarabine). Between 12/95 and

10/01, a total of 722 pts (median age 68 yrs) were randomized in four arms, as follows: G-CSF days 1-7 (during MICE, +/-; n=180), G-CSF days 8-%28% (after MICE, -/+; n=180), G-CSF days 1-%28% (during/after MICE, +/+; n=180), no G-CSF (-/-; n=182). After entering CR pts were scheduled to receive 2 courses of consolidation with the mini-ICE regimen (idarubicin, cytarabine, etoposide) given according to either an oral or an iv schedule (2nd randomization). Analyses were performed according to the intention-to-treat principle. Out of 687 eligible pts, 379 (55.2%) achieved CR: 54.7% (arm+/-), 50% (arm -/+), 65.9% (arm+/+), 50.3% (arm-/-), respectively. Pts randomized to receive lenograstim post-MICE (arms-/+ and +/+) had a CR rate of 57.9% vs 52.4% (P=0.18), but no fewer induction deaths (15% vs 12.4%). When given concomitantly to MICE (arms +/- and+/+), lenograstim resulted in a significantly higher CR rate (60.3% vs 50.1%, P=0.01), due to a reduction in both induction mortality (11.5% vs 15.9%) and resistant disease rate (27.4% vs 33.1%). Recovery of neutrophils >500/mmc was significantly faster in pts given lenograstim post-MICE (median 20 days vs 25 days, P<0.0001), and was accompanied by a reduction in the duration of hospitalization (median 26 days vs 29.5 days, P<0.0001); however, there was no difference in the frequency of grade 3-4 infections or in the number of fatal infections. Of the 379 complete responders, 279 have relapsed and 43 died while in CR. Median disease-free survival (DFS) was 9.5 months and the 3-yr DFS rate %17%.8%, with no significant difference between the treatment groups (arm -/+ and +/+ vs arm -/- and +/-, HR 0.99 (0.79, 1.23), P=0.90; arm +/-and +/+ vs arm -/- and -/+, HR 1.05 (0.84, 1.31), P=0.66). At a median follow-up of 4.7 yrs, a total of 611 pts have died. Median overall survival (OS) was 9.1 months and the 3-yr OS rate 16.3%, with no significant difference between the treatment groups (arm -/+ and +/+ vs arm -/- and +/-, HR 0.98 (0.84, 1.15), P=0.84; arm +/-and +/+ vs arm -/- and -/+, HR 0.91 (0.78, 1.07), P=0.24). In this trial of elderly AML, lenograstim improved clinical parameters of duration of neutropenia and hospital stay when given post-induction chemotherapy, but had no effect on infectious morbidity and mortality or survival. The higher CR rate observed in patients treated with G-CSF during MICE induction (arms +/- and +/+) may reflect enhanced sensitivity of cytokine-primed leukemic cells to the cytotoxic effects of chemotherapy, but the quality of these remissions remained poor since no gain in disease-free survival was noted.

1/7/7
DIALOG(R)File 5:Biosis Previews(R)

0014801831 BIOSIS NO.: 200400172588
Stem cell factor: Safety, efficacy, engraftment kinetics when used with G-CSF as a mobilizing agent in children who failed to be mobilized with G-CSF alone.
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ABSTRACT: Mobilization of peripheral blood stem cells with G-CSF (Filgrastim) alone or with chemotherapy has been a major advance in increasing the number of harvested haematopoietic stem cells. However some patients still fail to be mobilize sufficient stem cells for transplantation. Recombinant stem cell factor (rHuSCF) by itself has no direct mobilizing effect, but has been shown to increase mobilization 3-5 times when used with G-CSF. However the ability of rHuSCF to mobilize stem cells in children failing primary mobilization and its safety in children has yet to be determined. The efficacy of rHuSCF could be studied by comparing the mobilization yield with and without rHuSCF using pimary mobilization in the same patient as historical controls. We report the results of using rHuSCF along with G-CSF for mobilizing stem cells in 8 children from February 1999 to March 2003 who failed to be mobilized with G-CSF alone. The age of the children, 4 male and 4 female, ranged from 3 to %17% (median 9.5) years. 5 children had Neuroblastoma, 2 had relapsed Hodgkins disease and one had relapsed Anaplastic large cell lymphoma. Chemotherapy included Cisplatin, VP-16, Adriamycin for Neuroblastoma, COPE ABV for Hodgkins disease and mini-BEAM and ICE chemo for Anaplastic large cell lymphoma. All the patients were very heavily pretreated. G-CSF was administered as 10 microgram/kg/day sub cut for 4 days and continued during apheresis until a CD34 dose of 2X106/kg is obtained. Those who failed mobilization were treated with Filgrastim 10 microgram/kg/day sub cut along with Ancestim 20 microgram/kg/day sub cut for 5 days prior to apheresis. Premedication with diphenhydramine, salbutamol and ranitidine were used before administration of Ancestim. 6 children had local erythema and one child complained of feeling unwell without dysponea. None had anaphylaxis. In one child with neuroblastoma, primary mobilization using Filgrastim and Ancestim yielded a CD34 cell count of 9.38X106/kg. In another child with neuroblastoma, BM harvest achieved a nucleated cell count of 2.54X106/kg after mobilization with Filgrastim and Ancestim in contrast to CD34 of 0.09X106/kg in peripheral blood stem cells after primary mobilization with Filgrastim alone. In the other 6 children, mobilization using Filgrastim alone yielded a CD34 cell count 0.005 to 1.16X106/kg (median 0.135) as opposed to a CD34 count of 0.61-2.05X106/kg (median 1.65) after mobilization with Filgrastim and Ancestim. Using "t" test, paired two sample for means, we found the difference to be significant (p=0.001) using primary mobilization in the same patient as control. Conditioning protocols were Carmustine and VP-16 for Neuroblastoma, and CBV for Hodgkins disease and Anaplastic large cell lymphoma. G-CSF was administered from day +5 until ANC of 1.0X109/l is obtained. There was no graft failure. The median time to engraft (ANC.0.5X109/l) was 14.5 days (range 14-22) even though the median CD34 count 1.65X106/kg in those 6 patients mobilized with rHuSCF and G-CSF after failure with G-CSF alone. The other two patients that were transplanted (one after primary mobilization and the other with bone marrow) engrafted on days 14 and 16 respectively. Conclusion: Ancestim was safe and effective in mobilization along with Filgrastim in our cohort of children who failed primary mobilization with Filgrastim alone. Although our numbers are small, to the best of our knowledge it is still the first report on the use of stem cell factor for mobilization in children.

1/7/8
DIALOG(R)File 5:Biosis Previews(R)

0014801830 BIOSIS NO.: 200400172587
Safety and efficacy of allogeneic PBSC collection in normal pediatric donors: The pediatric blood and marrow transplant consortium experience (PBMTC) 1996-2003.
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ABSTRACT: Based on apparent safety and efficacy data from small clinical trials, healthy children increasingly are donating PBSC or DLI via apheresis for use by ill siblings. There is concern that PBSC collection may be more risky in pediatric donors, however, no large studies have assessed safety issues in this population. To address this need, we

reviewed 210 (205 PBSC, 5 DLI) collections (range 1-4d, median 1d) in 193 normal pediatric donors (8m to 17yr, median 11.8 yr) between the years of 1996-2003 at 20 institutions in the PBMTC. Donors received a median of 4 days of G-CSF and/or GM-CSF. The mean collection was 9.2X106 CD34+ cells/kg recipient weight. Using both forward and backward stepwise selection regression analyses on year of donation, donor age, donor weight, days of cytokine usage, and days of apheresis, only age (p=0.0006) and days of apheresis (p=0.0001) were found to be statistically significant for CD34+ cells/kg donor weight. The yield decreased with age and increased with collection days. As expected, the use of central venous access and sedation were common in younger children. Adverse events were mild and rare. Reported pain was more common in older donors and mostly treated with non-narcotic medications. Bleeding was rare and minimal, associated only with CVL placement or removal and controlled with direct pressure alone. One child developed a small hemothorax after subclavian line placement. Hypocalcemia symptoms included tingling, light-headedness, and fussiness in younger children. No other significant adverse events were noted. Most donors <20kg (23/25, 92%) required PRBC priming of the apheresis machine, compared to 2/32 (6%) of patients weighing between 20 and 30kg. No other patients received PRBC. More younger donors required overnight stays (age 0-6 43%, 7-12 23%, 13-%17% 4%) and had precautionary monitoring in the PICU (age 0-6 26%, 7-12 8%, 13-%17% 2%) than older donors. The majority of overnight stays were either for precautionary observation or for second day apheresis. Conclusions: This experience with over 200 collections demonstrates that PBSC collection is safe in normal pediatric donors and desired CD34 yields are easily achieved. Donors <7yrs may yield more CD34+ cells/kg donor weight than older donors. Children <20kg are generally exposed to the risk of PRBC transfusion for apheresis machine priming. Younger children also utilize more medical resources including anesthesia, CVL placement, use of the PICU for procedures, and overnight hospital stays.

1/7/79
DIALOG(R)File 5:Biosis Previews(R)

0014801827 BIOSIS NO.: 200400172584
The accelerated engraftment of peripheral blood cell counts following transplantation with hematopoietic stem and progenitor cells (HSCs) mobilized by the CXC chemokine GRObetaT (CXCL2DELTA4) is independent of homing to recipient bone marrow and the SDF-1alpha (CXCL12):CXCR4 migration axis.
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ABSTRACT: Mechanisms of homing and engraftment of hematopoietic stem cells (HSCs) are poorly understood. The chemokine receptor CXCR4 is expressed on primitive HSCs and the SDF-1alpha/CXCR4 axis has been implicated in HSC homing. In addition, the in vitro transmigration capacity of G-CSF mobilized CD34+ cells is associated with hematopoietic recovery. We reported that GRObetaT (CXCL2DELTA4) rapidly mobilizes HSCs, including long-term repopulating cells (LTRC) into peripheral blood in an equivalent fashion to G-CSF when used alone and synergizes with G-CSF when used in combination. Herein, we examined hematologic recovery of mice transplanted with HSCs mobilized by GRObetaT and G-CSF, their in vitro migratory potential towards SDF-1alpha and their marrow homing capacity post transplant in mice. Hematopoietic engraftment, defined by restoration of neutrophil (ANC) and platelet counts (PLT) occurs faster in mice transplanted with peripheral blood mononuclear cells (PBMCs) collected 15 minutes after a single dose of GRObetaT (2.5 mg/kg, SC) compared to cells mobilized by a multi-day regimen of G-CSF (50 ug/kg, bid, SC, X4 days). Time to ANC500 was 15 days ($p<0.05$) and time to 80% restoration of platelet counts (PLT80%) was 23 days ($p<0.05$) for mice receiving GRObetaT mobilized PBMC and %17% and 36 days for mice receiving G-CSF mobilized PBMC. ANC recovery was significantly improved in mice transplanted with PBMCs mobilized by the combination of a single dose of GRObetaT added to the G-CSF regimen (12.5 days, $P<0.05$), although PLT80% recovery was slower than observed with GRObetaT (29 days, $P<0.05$) but still faster than G-CSF. The PBMC mobilized by GRObetaT or G-CSF contained equivalent CFU-GM and CFU-GEMM, indicating that accelerated recoveries were not due to transplanted CFU number. In contrast, PBMC mobilized by GRObetaT plus G-CSF contained 7-8 fold more CFU-GM and 5-7 fold more CFU-GEMM that may have contributed to accelerated hematologic recovery. Transmigration of CFU-GM and CFU-GEMM in the c-kit+, lin- PBMC populations mobilized by GRObetaT or GRObetaT plus G-CSF to SDF-1alpha was significantly reduced compared to those in c-kit+, lin- PBMC mobilized by. G-CSF (77+-3% and 68+-4%, respectively for CFU-GM and 82+-0.4% and 71+-6%, for CFU-GEMM; $p<0.001$). Reduced migration to SDF-1alpha was not due to changes in CXCR4 expression. Homing of CFSE labeled mobilized PBMC into lethally irradiated recipient mice was not significantly different in any of the groups, however 35+-3% ($p<0.01$) fewer total CFU from GRObetaT mobilized PBMC were detected in the marrow of recipients after 24 hours compared to G-CSF mobilized PBMC, which is consistent with reduced migratory potential of CFU mobilized by GRObetaT to SDF-1alpha. Expression of L-selectin, VLA4 and VLA5 were reduced in GRObetaT mobilized c-kit+, lin- cells compared to cells mobilized by G-CSF and may contribute to reduced homing. These data indicate that the accelerated engraftment capability of HSCs mobilized by GRObetaT compared to HSCs mobilized by G-CSF is not due to increased numbers of transplanted short term repopulating cells, their homing/migratory potential, or adhesion molecule expression. Enhanced engraftment may result from selective mobilization of earlier LTRC or cells with an intrinsic capacity for accelerated engraftment and proliferation.

1/7/80
DIALOG(R)File 5:Biosis Previews(R)

0014801706 BIOSIS NO.: 200400172463
Low-dose total body irradiation (TBI) conditioning for hematopoietic cell transplants (HCT) from HLA-matched related (MRD) and unrelated (URD) donors for patients with hematologic malignancies: A five-year experience.
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ABSTRACT: Four-hundred fifty-three patients with hematologic malignancies were conditioned with a nonmyeloablative regimen that used 2 Gy TBI with or without fludarabine (30 mg/m2/dayX3 days) before and both donor and host cell immunosuppression via mycophenolate mofetil and cyclosporine after HCT from MRD (n=305) or URD (n=148). Forty-seven percent of

patients had aggressive advanced stage diseases (MRD 38%, URD 66%) and 20% had failed previous high-dose autologous or allogeneic HCT (16% of MRD; %28%% of URD). Diagnoses included ALL (n=10), AML (n=59), CLL (n=44), CML (n=37), HD (n=26), MDS/MPD (n=82), MM (n=116), and NHL (n=79). Transplants were done between 12/97 and 12/02. Patients enrolled in the multi-institutional studies were either too old or, if younger, had significant medical contraindications to conventional HCT. Median patient age was 55 (range 5-74) years, and median follow-up was 696 (range 82-1795) days among survivors. Four percent of patients received marrow (all URD), and 96% received unmodified G-CSF-mobilized peripheral blood cells containing median doses of 7.44X106 CD34 and 3.27X108 CD3 cells/kg. Median percentages of donor chimerism on days %28%, 56 and 84 of CD3 cells were 85%, 92%, 95%; for CD33:96%, 100%, 100%; and of marrow: 95%, 97%, 98%, respectively, with no differences between MRD and URD recipients. Sustained donor engraftment occurred in 92% of patients (MRD 95%; URD 84%). Acute GVHD grades II, III and IV occurred in 34%, 10% and 4% of patients, respectively (MRD: 31%, 10% and 5%; URD: 42%, 9% and 3%). Forty-four percent of patients had chronic GVHD requiring therapy (MRD 43%; URD 45%). Of the 332 patients with measurable disease at the time of HCT, 56.5% achieved disease responses (CR 49%, PR 7.5%). Disease responses were seen across all disease categories. Day 100 nonrelapse mortality was 7% (MRD 5%; URD 11%). Overall, the 2-year Kaplan-Meier estimate of relapse-related mortality was 26% (MRD 23%; URD 32%), and non-relapse mortality was 22% (MRD 22%; URD 22%). Causes of death contributing to nonrelapse mortality are given. The rates for 2-year overall and progression-free survival were 51% and 37%, respectively (MRD 54%, 40%; URD 45%, 31%). Results from these studies of nonmyeloablative conditioning regimens using low-dose TBI for HCT in both MRD and URD recipients are encouraging. Less toxic regimens can be implemented while preserving potent graft-versus-tumor (GVT) effects. Current challenges include controlling graft-versus-host disease (and infectious complications) while allowing a GVT effect to occur to reduce the risk of relapse. Such strategies would expand treatment options for patients who would otherwise be ineligible for potentially curative therapy with allogeneic HCT.

1/7/81
DIALOG(R)File 5:Biosis Previews(R)

0014795035 BIOSIS NO.: 200400162376
Treatment and outcome of children with acute lymphoblastic leukemia belonging to Jehovah's Witnesses: A survey of 20 years.
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ABSTRACT: Jehovah's Witnesses generally refuse transfusion of blood or its major components for religious convictions and would even accept death by rejecting this potentially life-saving intervention. Therapy of malignant tumors in these patients by current multimodality treatment remains an ongoing challenge to all persons involved. Especially, treatment of acute leukemia requires aggressive polychemotherapy regimens necessitating transfusional support in virtually all patients. We report here the experience with pediatric Jehovah's Witnesses patients suffering from acute lymphoblastic leukemia (ALL) with respect to transfusional policy and outcome. Data of children with ALL belonging to Jehovah's Witnesses were obtained by specific questionnaires sent out to all clinics participating in the ALL-BFM studies. 70 of 84 clinics (response rate 83%) reported 53 patients with all kind of malignant pediatric tumors. Among these, 27 children with ALL (18 boys, 9 girls) were treated in 21 institutions between 1981 and 2003. Median age at diagnosis was 8.0 years (range, 0.4-16.2). Immunophenotype was B-cell derived in 77% and T-cell derived in 23%. Risk group allocation was as follows: standard risk group 37%, middle risk group 46% and high risk group %17%%. Chemotherapy was modified in six cases according to the physicians' discretion (e.g. reduction of anthracyclines in induction therapy) and no randomization was performed in eight patients. Treatment schedule was delayed in seven patients. Institutional transfusion thresholds were lowered for all children as far as possible. Minimal median value for hemoglobin and platelets in this cohort were 4.6 g/dl (range, 2.6-7.0) and 10/nl (range, 1-312), respectively. One girl developed a hematothorax after central venous catheter insertion but fully recovered, and one boy died from bleeding and infection due to relapse treatment. Erythropoietin was given to patients (all diagnosed since 1991) with doses from 100 to 400 units/kg body weight. Treatment duration and number of weekly applications varied. Further supportive therapy included fresh-frozen plasma and G-CSF in a subset of patients. Ultimately, 16 patients (59%) received red blood cells (11 of these with concomitant erythropoietm application) and 12 (44%) were given platelet transfusions. Blood transfusions were generally rejected by the parents and were declined but tolerated in seven patients. Transfusion had to be legally enforced in eight patients. At the time of last contact, 21 patients were in first complete remission, six had relapsed and seven died (five of their disease, two unknown). Refusal of blood components by Jehovah's Witnesses comprises an essential part of their belief. Despite lowering thresholds for transfusion, treatment could be safely performed for the majority of patients. The recent distinction between primary (unacceptable) and secondary (acceptable) blood components, formation of a reform movement within Jehovah's Witnesses (AJWRB) allowing a more liberal transfusion policy and the fact that parents more often agree with transfusion for their children than for themselves point to a doctrinal shift concerning transfusional policy.

1/7/82
DIALOG(R)File 5:Biosis Previews(R)

0014795031 BIOSIS NO.: 200400162372
The combination of cladribine with cytarabine and G-CSF (CLAG) or CLAG with mitoxantrone (CLAG-M) as induction therapy in primary resistant or relapsed acute myeloid leukemia: Polish adult leukemia group (PALG) Study.
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ABSTRACT: Here we present the efficacy and toxicity of CLAG/CLAG-M regimen in refractory or relapsed acute myeloid leukemia (AML) patients. Induction chemotherapy consisted of 2-CdA 5 mg/m2 in 2h infusion, Ara-C 2 g/m2 in 4h infusion 2h after 2-CdA (days 1-5) and G-CSF 300 mg sc (days 0-5) (CLAG). Some patients received mitoxantrone additionally at the dose of 8 mg/m2 iv on day 1 (CLAG-M). In case of PR second identical course was administered. Refractory AML was defined according to the following criteria: (1) primary resistance to initial induction therapy, (2) first

early relapse with a CR1 duration of less than 6 months, (3) second or subsequent relapse, (4) relapse after SCT. 82 patients in the median age of 45 years (range, 18-70 years) from 9 centers were registered. Refractory AML was diagnosed in 72 patients and relapsed AML with CR1 of more than 6 months duration was diagnosed in 10 patients. Six patients had MDS preceding AML. Karyotype analysis was performed in 47 patients, 6 patients had favorable, 30 intermediate, 6 unfavorable and 5 patients had cytogenetic abnormalities of unknown prognostic significance according to SWOG criteria. 67 patients received CLAG and 15 patients CLAG-M regimen as induction treatment. 42 out of 82 patients (51%) achieved CR, 27 (33%) were resistant and 13 (16%) died early. 35/72 (48%) of refractory AML patients achieved CR and 7/10 (70%) in the group of AML patients relapsed after CR1 of more than 6 months in duration, 35% and 20% were refractory to CLAG/CLAG-M regimen in both groups, respectively, and %17%% and 10% died early. 5 out of 6 patients with MDS preceding AML achieved CR (80%). There were no significant differences in the CR rates between CLAG and CLAG-M regimen (51% vs 54%, p>0.05). Hematological toxicity was the most prominent toxicity of the treatment, the median duration of profound neutropenia (ANC <0.5 G/l) was %17% days, thrombocytopenia (plt <20 G/l) 13 days and the median time of hospitalization was %28% days. The hematological and non-hematological toxicity of CLAG and CLAG-M regimen were also similar. Median OS for the group of patients in CR was 59 weeks (range, 3.5-2065 weeks) and median DFS was 16 weeks (range, 1-2027 weeks). Median OS for patients refractory to CLAG/CLAG-M regimen 23 weeks (range, 8-1337 weeks). Following prognostic factors for CR probability were analyzed: age, WHO performance status, % of blasts in the bone marrow, WBC at diagnosis and karyotype. None of this factors influenced significantly the CR probability. We conclude that CLAG/CLAG-M has high activity in refractory AML patients. Its promising activity in the group of 10 patients with relapsed AML after a CR1 longer than 6 months in duration as well as in the group of 6 patients with MDS preceding AML deserves further observation.

1/7/83
DIALOG(R)File 5:Biosis Previews(R)

0014795003 BIOSIS NO.: 200400162344
Glivec in combination with HA regimes for treatment of 20 patients with Ph Chromosome postive acute leukemia.
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ABSTRACT: OBJECTIVE: Glivec was approved by Food & Drug & Administrats (FDA) in May 2001 as a gene target drug for treatment of Chronic Myeloid Leukemia (CML) and showed a good curative effect for patients with chronic myeloid leukemia chronic phase. But it was worse in Patients with CML blast phase treated with alone Glivec. Glivec was reported having cooperation effect with other chemical agents in vitro, but there is few report in clinic combined application. In this paper, we analyzed effectiveness of glivec in combination with homoharringtonine (HHT) and cytarabine (Ara-C) for patients with Ph Chromosome postive acute leukemia (Ph+-AL); and investigated patients' tolerance to side effect of this trial. METHODS: A total of 20 patients, (16 males, 4 females, median age: 43 years) was eligible. Blasts in patients Peripheral Blood (PB) or Bone Marrow (BM) were more man 30%, bcr/abl fusion genes were detected positive in 90% cells by analysis of karyotyping or Fluorescence in situ hybridization (FISH). 5 patients showed t(9;22), other 15 patients showed more complicated chromosome abnormal. Of these 20 patients, %17% patients developed Ph+-ANLL from CML, 1 case developed Ph+-ALL, and other 2 cases were primary Ph+-ALL. The median interval from diagnostic to Glivec treatment was 4 months. 18 of 20 patients received different chemotherapy regimes for 2-4 cycles, but nobody were Hematologica Complete Remission (HCR). All patients were given oral Glivec daily at a dose of 0.3-0.6 in a median time 2.5 months (range, 1-6.5 months). Ph+-ANLL patients were infused with HHT over 6-24 hours daily at dose of 1-2mg intravenously and Ara-C 30-50mg daily subcutaneously for 10-14 days; 3 patients with Ph+-ALL received HOAP or DOP combination treatment regimens (One cycle consists of HA with a same dosage described above for Ph+-ANLL patients for 7 days, daunorubicin at a dose of 40mg/d intravenously for 3 days, vincristine at 2 mg/wk dose for two weeks, and prednisone at 60-80mg/d dose for 14 days). Median treatment cycle was 2 (1apprx3). The dosage of Glivec could be reduced or treatment was suspended when bone marrow inhibition happened. G-CSF would be used when necessary. The curate effect was evaluated by international hematology and cytogenetics standards, in which bone marrows were examined every chemotherapy cycles and chromosomes were analyzed 3 months later. RESULTS: Among the 20 patients receiving Glivec, 40% patients achieved HCR, and 25% patients achieved Hematologincal Partial Remission (HPR), but only 15% patients approached a partial cytogenetic remission and no cytogenetic responses were found in other 85% patients. WBC in PB reduced from 41+-31X109/L to normal level. The blasts decreased from (0+-30)% to (1.9+-2.9)% (p<0.001) in median time 21.0+-16.8 days. 3 patients with high fever recovered normal temperature after 3 days treatment. 2 patients receiving Glivec at dose 0.6/d presented pleurorrhea and serious edema on 5th day. 20 patients showed 90% suppression on BM. All of them experienced bacteria infection and recovered from antibiotic treatment. Relapse rate was 50% and total survival rate was 95% when follow-up median time at 3 months; but when follow-up median time at 8 months, total survival rate reduced to 40%, the rate of death and lost follow-up patients added to 60%. The most common side effects included nausea, vomiting, limited edema, and muscle convulsion, but it can be tolerated without special dealing. CONCLUSION: Regimen of Glivec in combination with HA could increase chemotherapy effect among patients with Ph+-AL, extend their lives and show tolerance to side-effect, except for a poor cytogenetic response.

1/7/84
DIALOG(R)File 5:Biosis Previews(R)

0014794548 BIOSIS NO.: 200400161889
Clinical efficacy and prediction of response to granulocyte transfusion therapy from G-CSF and dexamethasone-stimulated donors into patients with neutropenia-related infections.
AUTHOR: Lee Je-Jung (Reprint); Song Ho-Chun; Chung Ik-Joo (Reprint); Kim Yeo-Kyeoung (Reprint); Byun Jeong-Rae (Reprint); Bom Hee-Seung; Cho Duck; Ryang Dong-Wook; Kim Hyeoung-Joon (Reprint)
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ABSTRACT: Neutropenia-related infection is a major factor contributing to morbidity and mortality in patients with hematologic malignancy despite appropriate antimicrobial agents. Granulocyte transfusions have been advocated by some for the treatment of severe, progressive infections in the neutropenic patients who fail to respond to antimicrobial agents. In granulocyte transfusion therapy, it is necessary to establish the optimal doses and administration schedule of the mobilizing agent, as well as the clinical efficacy and safety of transfusion therapies. This prospective

study evaluated the safety and efficacy of transfusing granulocytes, which were obtained with a combination of G-CSF and dexamethasone, into 27 patients with neutropenia-related infections. Four patients underwent 99mTc-HMPAO-granulocyte scintigraphy during the infusion of the granulocytes. Leukapheresis was performed 115 times, to give a mean yield of 8.1X1010 granulocytes (range: 2.1-%17%.9X1010). Seventeen patients (63%) responded to the granulocyte transfusion therapy, while there were 10 (37%) non-responders. In terms of patients with identified infections, favorable responses were seen in 83.3%, 62.5%, and 50.0% of the patients who were infected with fungi, Gram-negative and Gram-positive bacteria, respectively (P=0.04; P=0.95; P=0.29, respectively). Most of granulocyte transfusions were well tolerated except 1 case each of arrhythmia and pulmonary edema. Granulocyte scintigraphy showed abnormal early uptake and persistent retention in patients who showed favorable responses to therapy. In contrast, there was no uptake in the lesions of patients who did not respond to therapy. This study showed that the combination of G-CSF and dexamethasone is effective in mobilizing the granulocytes of normal healthy donors for use in granulocyte transfusion therapy, and that granulocyte transfusion therapy may be useful adjuvant therapy for treating neutropenic patients with fungal infections that are resistant to antimicrobial agents. Furthermore, 99mTc-HMPAO-granulocyte scintigraphy, which is used to measure granulocyte uptake at the focus of infection, may be useful in predicting responses to granulocyte transfusion therapy.

1/7/85
DIALOG(R)File 5:Biosis Previews(R)

0014793982 BIOSIS NO.: 200400161323
Combined infusion of peripheral blood stem cells (PBSC)+bone marrow (BM) in poorly mobilizing patients undergoing high-dose therapy (HDT) and autologous stem cell transplant (ASCT).
AUTHOR: Comeau Terrance (Reprint); Serody J; Gabriel D A; Wiley J; Kirby S; Irons R; Hill D; Tuttle R; Wilson C; Kok B; Bandarenko N; Brecher M E; Shea T C
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ABSTRACT: A minimum PBSC product of 2X106 CD34 cells/kg should be infused following HDT and ASCT to ensure rapid platelet (PLT) and neutrophil (N) recovery. Failure to infuse this amount results in delayed engraftment with increased transfusion requirements, increased morbidity, and longer length of hospital stay. Repeat mobilizations with different regimens have been variably successful but rarely result in a higher yield than that obtained with the first attempt. From 1992 to 2003, 95 pts at our center have received combined PBSC and BM as autologous stem cell support following HDT. We have evaluated the outcome of 67 of those pts whose combined yield of CD34+ cells were <3X106 CD 34 cells/kg and who failed to mobilize >2X106 CD34+ PBSC utilizing G-CSF or chemotherapy-based regimens. The patient population consisted of 39 females and %28% males ranging in age from 9 to 64 years with a median age of 49 years; the diseases for which HDT was carried out consisted of Breast cancer (10 pts), Hodgkin's disease (11 pts), NHL (27 pts), AML (4 pts), Ovarian cancer (11 pts), and Multiple Myeloma (4 pts). A minimum of 1X108 Total Nucleated Cells (TNC) was harvested from the BM of these pts under general anesthesia. After HDT, all pts were infused with both mobilized PBSC and BM. We have evaluated the outcome of these pts by dividing them into 4 groups based on the CD34 content of the combined graft. Results of engraftment of these quartile (Q) groups are shown below. As expected, the times for PLT and N engraftment were decreased from a median of 34 and 13 days (d) respectively in Q1 (median 0.67 million CD34/kg) to 13.5 and 11 d respectively for Q4 (median 2.595 million CD34/kg). In addition, the range for PLT engraftment also decreased as the CD34 content of the graft increased: 16-185 d in Q1 compared with 5-62 d in Q4. Kruskal-Wallis one way analysis of variance on ranks revealed that the median PLT engraftments were statistically different among the 4 groups (p=0.003). Analysis with pairwise multiple comparison procedures using Dunn's methods revealed that PLT engraftment in Q1 was not statistically different than that in Q2 but was statistically different from Q3 and Q4 (p<0.05). There was no correlation between TNC dose or total mononuclear cell dose with any engraftment parameters. Despite the low CD34 content of the graft in Q1, <20% of pts required PLT transfusions beyond day 50 post-transplant compared with 6% of pts in Q2-Q4. Only 3% of pts receiving a CD34 dose >1.5 million/kg required PLT transfusion beyond day 50 compared with 15% of pts with grafts containing a lower CD34 content. This data suggests that the addition of BM to a PBSC product with a low CD34 content provides a safe and effective alternative for the majority of pts with low PBSC products following their initial mobilizations and can result in lower PLT transfusion requirements.

1/7/86
DIALOG(R)File 5:Biosis Previews(R)

0014793980 BIOSIS NO.: 200400161321
Reduction of the aplastic phase and hospitalization in patients receiving PBSC autotransplantation followed by Erythropoietin plus filgrastim: A matched analysis of 79 consecutive procedures.
AUTHOR: Olivieri Attilio (Reprint); Scortechini Ilaria (Reprint); Capelli Debora (Reprint); Montanari Mauro (Reprint); Lucesole Moira (Reprint); Gini Guido (Reprint); Cecchi Stefano (Reprint); Spitaleri Luca (Reprint); Troiani Emanuela (Reprint); Masia Maria Cristiana (Reprint); Leoni Pietro (Reprint)
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ABSTRACT: We compared engraftment kinetics and clinical course in 65 consecutive Lymphoma or Multiple Myeloma patients, receiving PBSC autotransplant followed by early administration of alpha-Erythropoietin(EPO)+filgrastim(G-CSF) (groupB) or delayed G-CSF alone (group A). We evaluated the duration of aplastic phase, fever, antibiotic therapy, and hospitalization, the transfusional need and the costs of the transplant procedure. All patients received HDT including High Dose Melphalan (HDM) alone (200 mg/sm) in those affected by MM (26), or in combination (BEAM regimen) in those affected by NHL (39); the median age was 60 years. 33 patients received delayed G-CSF at 5 gamma/kg/day subcutaneously (s.c.), from day +5 after PBSC reinfusion untill ANC >2000/mcl (group A), while 32 patients, received the early administration of G-CSF 5 gamma/kg/day s.c. plus EPO 10,000 U/day s.c., from day +1 (group B). 14 patients received double autotransplant for a total of 40 HDT procedures in group A and 39 HDT procedures in group B; the two groups were matched for the clinical characteristics and for the number of CD34+/kg reinfused. The hemopoietic reconstitution was significantly faster in group B, with 10 days to achieve ANC >500/mcl, compared to 11 days in group A; the thresholds of PLT count >20000/mcl, >50000/mcl, >150000/mcl were achieved on day +13,+%17% and +23 respectively in group B, compared to day +14, +24 and +50 respectively, in group A. The median duration of severe neutropenia was significantly shorter in the group B compared to group A, since duration of neutropenia <100/mcl was 3 days (CI 0-6) in group B vs 5 days (CI: 1-22) in group A

(p<0.0001); duration of neutropenia <500/mcl was 5 days (CI 1-9) in group B vs 7 days (CI 3-23) in group A (p=0.001). The transfusional need was almost abolished in the group B, with 0 RBC units transfused (0-61) versus 2 (0-8) in the group A and 1 PLT unit transfused in group B (0-5) versus 2 (0-9) in the group A. The clinical course was significantly better in group B in terms of days of fever (1 in group A versus 0 in group B, p=0.01), days of i.v. antibiotic therapy (1 in group A versus 0 in group B, p=0.01) and days of hospitalization from reinfusion (14 in group A versus 2 in group B, p<0.0001). The early combination of G-CSF+EPO significantly improved PLT and PMN engraftment kinetics, since 90% of patients achieved ANC >500/mcl on day +14 in the group A vs+11 in group B and the 90% of patients achieved PLT >50000/mcl on day +37 in the group A, vs +22 in group B. The mean cost of transplantation procedure was 24,426 Euro in group A vs 18,560 Euro in group B and this was due to the reduction of the hospital stay (mean indirect costs reduction=3360 Euro), and of the direct costs (mean direct costs saving=2506 Euro). Overally a mean cost saving of 24% was observed for each transplant procedure in group B, despite the major use of some expensive drugs, such as EPO and the larger use of G-CSF. Our study shows that the early administration of EPO+G-CSF not only accelerates the engraftment kinetics, but also significantly improves the clinical course of transplant; this leads to a significant cost reduction and could make feasible an outpatient Transplant Program for MM and NHL patients, conditioned with HDM.

1/7/87
DIALOG(R)File 5:Biosis Previews(R)

0014793979 BIOSIS NO.: 200400161320
CD34+ selection of autologous transplants following myeloablative therapy in patients with newly diagnosed myeloma shows no significant clinical benefit at 4 years: An EBMT phase III randomized Study.
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ABSTRACT: CD34+ selection of PBSC has been used in MM as a mean to reduce relapse linked with tumor cells contamination and thus improving outcome. However, a clinical benefit has not been demonstrated at the onset of this study. From May 1995 to November 1999, 127 pts from %17% EBMT centers with newly diagnosed advanced MM were included into this phase III trial and 112 pts are analysed. Responders to 3 cycles of VAD were randomized to receive a CD34+ selected graft (arm A, n=57) or an unselected graft (arm B, n=55). PBPC were harvested following mobilization with cyclophosphamide 4g/m2 and G-CSF (Filgrastim). Conditioning regimen in both arms was TBI and melphalan 140 mg/m2. CD34+ selection was performed in arm A using the CellPro Ceprate-SC device and resulted in a median purity of 88.5% and yield of 63%. Molecular analysis showed a median tumor cell depletion of 1.93 log (0.87-5.2). The median number of CD34+ cells reinfused was 7.2X106 CD34 cells/kg (1.4-50.4) in arm A and 14.4X106 CD34 cells/kg (1.8-99.2) in arm B. The median time to neutrophil engraftment (ANC >O.5X109/l) was 10 days in arm A (8-14) and 10 days in arm B (8-21). The median time to platelets engraftment (plts >20X109/l) was 11 days in both arms but one patient in arm A never reached 20X109/l platelets without supportive transfusions. 13 episodes of serious infections between the time of neutrophil engraftment and day 100 were reported in arm A compared to only 1 in arm B. All infections were viral except 1 bacterial and 1 protozoal. For 3 patients in arm A, these infections were fatal (parainfluenza, CMV and myocarditis of infective etiology). The overall transplant mortality was 2.7% (3 patients in arm A). There was no significant difference in CR rate at 1 year as defined by EBMT/IBMTR/ABMTR criteria (16% in arm A and 15% in arm B). There is so far no significant difference in EFS and OS. Median follow-up is 47 months in both arms. Probability of OS at 3 years is 71% in arm A and 81.5% in arm B. The 3 year relapse risk is 54.05% in arm A vs. 30.5% in arm B. In summary, CD34+ selection resulted in a 1.9 tumor cell depletion without delay in hematological recovery. However, long term follow up analysis of these patients shows no significant clinical benefit for progression free survival. Moreover, the increased incidence of bacterial and viral life threatening infections in the CD34+ selected arm, similar to those for allogeneic BMT recipients, legitimate systematic prophylaxis regimens and raise clinical concerns. Altogether, these results suggest new approaches in CD34+ selection to circumvent immune recovery delay.

1/7/88
DIALOG(R)File 5:Biosis Previews(R)

0014793978 BIOSIS NO.: 200400161319
Infusion of higher CD34+ cell doses in stem cell products is associated with inferior progression-free survival (PFS) after autologous hematopoietic stem cell transplantation (AHSCT) for relapsed and refractory aggressive non-Hodgkin's lymphoma (NHL).
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ABSTRACT: High-dose therapy and AHSCT is the standard of care for patients with relapsed or refractory aggressive NHL that is responsive to salvage chemotherapy. However, more than 50% of patients with chemosensitive aggressive NHL will experience disease progression after AHSCT. An augmented high-dose regimen of cyclophosphamide 7,200 mg/m2, carmustine 300-400 mg/m2, and etoposide 2400 mg/m2 (CBV) was developed in an attempt to improve disease control post-transplant. Sixty-seven patients (35 men, 32 women) received this regimen followed by infusion of unpurged autologous peripheral blood stem cells mobilized by G-CSF alone (27 patients) or cyclophosphamide plus G-CSF (40 patients). The median age was 52 years (range, 23 to 72 years). Forty-nine patients had diffuse large B cell lymphoma (10 transformed from indolent NHL), 5 had Burkitt lymphoma, 4 had anaplastic large cell lymphoma, and 9 had other aggressive subtypes of NHL. Thirty-seven patients had relapsed after standard chemotherapy, %28% patients had primary refractory disease, and 2 patients had transformed lymphoma in first partial response. Treatment-related mortality was 4%; no unanticipated severe toxicities were observed. Actuarial 4 year overall survival and PFS were 46+-8% and 36+-6%, respectively. PFS of patients with relatively chemorefractory disease (defined as 25 to 49% reduction in tumor volume after salvage chemotherapy) was no different than that of patients with chemosensitive disease (P=0.272). In multivariate analysis, independent risk factors for disease progression post-transplant were histologic involvement of marrow by lymphoma at diagnosis and/or relapse and infusion of increased numbers of CD34+ cells per kg in the stem cell autograft. PFS at 4 years was 47+-9% for patients without marrow involvement as compared to 12+-8% for patients with marrow involvement by lymphoma (P=0.018). Patients with

progressive disease post-transplant had received 6.15+-5.37X106 CD34+ cells per kg in the autograft, as compared to 3.29+-2.04X106 CD34+ cells per kg received by patients who survive progression-free (P=0.007). This result contrasts markedly with the robust association between higher graft cell doses and improved outcome after allogeneic stem cell transplantation. We hypothesize that, in the setting of autologous transplantation, a negative effect of infusing larger cell doses nullifies the beneficial effects on engraftment. Regimens that mobilize CD34+ cells have been shown to also mobilize lymphoma cells in vivo, so it is possible that infusion of larger numbers of clonogenic lymphoma cells in the autografts of some patients contributed to disease progression post-transplant. Moreover, the strong association between marrow involvement and inferior PFS suggests that it is rational to investigate the role of in vitro or in vivo purging of the autografts. PFS of patients receiving this and other augmented CBV regimens does not appear to be substantially better than PFS of patients receiving standard high-dose CBV regimens. Novel approaches, such as post-transplant immunotherapy, should be undertaken to improve the outcome of AHSCT for patients with relapsed and refractory aggressive NHL.

1/7/89
DIALOG(R)File 5:Biosis Previews(R)

0014793973 BIOSIS NO.: 200400161314
Immunoablative therapy with autologous stem cell support in the treatment of 25 patients with poor risk multiple sclerosis.
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ABSTRACT: The immunoablative therapy with hematopoietic stem cell transplantation represents an encouraging method for patients with intractable form of multiple sclerosis (MS). Thirty patients with poor risk MS were included in the phase I/II clinical trial involving the high dose chemotherapy with autologous peripheral blood progenitor cell (PBPC) rescue. Twenty five patients underwent high dose conditioning BEAM with at least 2 months of follow up. T cell depletion in vitro was performed in 16 grafts. Nine patients with not purged graft received in vivo ATG 4mg/kg i.v. D+1, D+2 after transplantation. In 3 patients PBPC mobilization failed (cyclophosphamide 4g/m2+G-CSF). One patient refused transplantation after improvement in disability following mobilization. Median follow-up is 30 months (2-64). Median EDSS (Expanded Disability Status Scale) of grafted patients at the time of inclusion were 6.5 (5.0-8.5), median EDSS of grafted patients at the last follow up was also 6.5 (5.0-10.0). Two patients out of 25 (8%) improved significantly (by gtoreq1.0 point on EDSS), 7 patients (%28%%) improved not significantly (by 0.5 point). Ten patients (40%) did not change their EDSS. Four patients (16%) gained their disability significantly (by gtoreq1.0 point on EDSS) despite the treatment, one of them died 31 months after the transplantation from disease progression (EDSS 10.0). Two other patients (8%) worsened not significantly (by 0.5 point) on their EDSS. Patients who stabilized their disability or improved represent 76%. Changes between the EDSS before and after the transplantation in the group were not significant (Wicoxon's, repeated measure ANOVA, t-test). The development of disability between the group that was grafted with in vitro purged graft and the group with ATG i.v. was also not significant (Wilcoxon's, Mann-Whitney). Among 4 mobilized but not transplanted patients 1 improved by 1.5 point on EDSS, one stabilized, 2 patients worsened by 1.0 and 0.5 respectively. Twenty patients stabilized their MRI finding, in 2 patients decreased number and size of lesions were detected, 3 patients worsened their MRI. No mortality has been observed in this cohort. However, the toxicity of the transplantation differed in each individual; two serious events have been observed. The first was respiratory failure after the onset of mucositis in the patient with severe pontomesncephalic impairment, the second one was sepsis with respiratory failure following bilateral pulmonary hemorrhage. Both patients needed temporary artificial ventilation. Changes in lymphocyte subsets in peripheral blood were followed before and after the treatment. Twelve months after the transplantation percentage of CD4+ cells and CD4+CD45 as well as IRI are still significantly decreased. As the significant majority of patients at least stabilized in their disability, we consider the results to be promising. Next patients will be included in the new international randomized clinical trial (ASTIMS).

1/7/90
DIALOG(R)File 5:Biosis Previews(R)

0014793966 BIOSIS NO.: 200400161307
Phase I/II trial of dose escalation of melphalan (MEL) with amifostine (AMI) cytoprotection supported by autologous hematopoietic stem cell transplant (HSCT) in multiple myeloma (MM) patients gtoreq65 years.
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LANGUAGE: English
ABSTRACT: There is an increased interest in utilizing high dose therapy with autologous (HSCT) transplant in MM patients gtoreq65 years. Review of the literature indicates that some studies report similar safety and efficacy of HSCT compared to younger patients (<60 and gtoreq60; Reece et al Bone Marrow Transplant, in press) whereas other studies indicate that older patients have higher morbidity and mortality, especially those treated with MEL 200 mg/m2 over the age of 70 (Badros et al Br J Haematol 114:600, 2001). We have previously shown that MEL can be dose-escalated to 280 mg/m2 when combined with AMI as a cytoprotectant agent (Reece et al Blood 100:432a, 2002). To determine the maximum tolerated dose (MTD) of high dose MEL with AMI as a cytoprotection in elderly (gtoreq65 years) MM patients, we conducted a Phase I/II trial of AMI 740 mg/m2 on days -2 and -1 with MEL 150 mg/m2 (on day-1) with increases by 20-25 mg/m2 in cohorts of 4 patients. A total of %17% patients have been enrolled as of August 1, 2003. The median age of the entire study was 69.4 yrs (65-74). Pre-transplant disease status: 4(24%) refractory relapse, 2(12%) chemosensitive relapse, 6(35%) primary refractory disease, 4(24%) PR and 1(5%) CR. A minimum of 2X106 CD34+ cells/kg was required to proceed to HSCT. Stem cell mobilization included: G-CSF alone (n=3), cytoxan 2.5 g/m2 n=7), cytoxan 3g/m2/etoposide 0.5g/m2 (n=5) and more than one mobilization attempt (n=2). The median number of CD34+ cells/kg infused was 6.18X106 (range 2.1-32.39X106). Time to engraftment, toxicities and duration of hospitalization are provided. The MTD for MEL was 220 mg/m2 at which dose one patient had 3 grade 3 toxicities (cardiac arrhythmia, mucositis and enteritis) and 1 patient had one grade 3 (atrial fibrillation) toxicity. At day 100 post transplant, of the 15 evaluable patients (2 patients too early), there were 3 (20%) CRs, 10 (67%) PRs and 2(13%) non responders. With a median follow up of 10 months, the event

free and overall survivals are 60% and 82% respectively. High dose MEL can be safely administered to patients gtoreq65yrs with response rates comparable to those seen in younger patients treated at our institution. The on-going Phase II study is being conducted at MEL 200 mg/m2. The toxicities, EFS and OS will be compared to patients ltoreq65yrs serving as historical controls without AMI cytoprotection.

1/7/91
DIALOG(R)File 5:Biosis Previews(R)

0014793962 BIOSIS NO.: 200400161303
The ability to harvest increased numbers of peripheral blood progenitor cells is a predictor of improved overall survival in patients with multiple myeloma treated by autologous hematopoietic stem cell transplantation.
AUTHOR: Fraser Graeme (Reprint); Meyer Ralph (Reprint); Marcellus Deborah (Reprint); Benger Ann (Reprint); Kouroukis C Tom (Reprint); Foley Ronan (Reprint)
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ABSTRACT: High dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) is currently recommended as standard practice for eligible patients diagnosed with multiple myeloma (MM). Infusion of an optimal peripheral blood progenitor cell (PBPC) dose (defined as 5X106 CD34+ve cells/kg) is associated with timely engraftment of red cells, platelets, and neutrophils. Recent evidence suggests that increased PBPC dose may predict a favorable prognosis in patients undergoing autologous HSCT for non-Hodgkin's and Hodgkin's lymphoma. We have evaluated the effects of increased PBPC dose in patients with MM utilizing a retrospective cohort design. We evaluated 108 consecutive patients referred to our institution for autologous HSCT between October 1997 and January 2002. Of these, 69.4% proceeded to transplant and comprised the cohort for analysis (N=75). Median age of patients was 57 years. Patients received 4-6 cycles of Vincristine, Adriamycin, and Dexamethasone (VAD) chemotherapy prior to HSCT. For PBPC mobilization, patients received a standardized protocol consisting of cyclophosphamide (2.5 gm/m2) and G-CSF (10mug/kg) followed by planned, large volume (25L) apheresis on day 11. A second collection was performed on day 12 if <5X106 CD34+ve cells/kg were obtained on the first harvest day. Most patients (89.6%) successfully mobilized >5X106 cells/kg in a single harvest. Patients mobilizing greater than 10X106 CD34+ve cells/kg (increased PBPC dose) were compared to those mobilizing less than 10X106/kg. Known prognostic factors included in Cox proportional hazards models were determined a priori. The mean number of CD34+ve cells collected for infusion was %17% .89X106/kg (range 3-73X106/kg) and 66% of patients mobilized greater than 10X106/kg. Median duration of follow-up was 1.7 years. Following multivariate analysis, increased PBPC dose was strongly associated with improved overall survival (p=0.002). No other factors included in the analysis achieved significance (age, Durie-Salmon stage at diagnosis, IgA vs. non-IgA MM, response to VAD, time from diagnosis until HSCT, and conditioning with melphalan vs. melphalan plus TBI). B2-microglobulin and G-banding cytogenetic assessments are not routinely performed at our center and could not be included in multivariate analysis. No patients underwent tandem autologous HSCT. Four year overall survival for patients in the increased PBPC dose group was 78.4% compared to 31.0% in those patients mobilizing less than 10X106/kg. We conclude that the ability to mobilize increased doses of PBPC's is an independent predictor for improved survival in patients with MM treated with autologous HSCT. This information may be of clinical use in determining post-transplant treatment options.

1/7/92
DIALOG(R)File 5:Biosis Previews(R)

0014793946 BIOSIS NO.: 200400161287
Poor stem cell harvests increase the risk of myelodysplastic syndrome and/or acute myelogenous leukemia (MDS/AML) following autologous stem cell transplant (ASCT).
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ABSTRACT: From 1/93 through 12/01, we treated 526 patients (pts) for either Non-Hodgkin's Lymphoma (NHL) or Hodgkin Disease (HD) with busulfan, VP-16, and cyclophosphamide followed by ASCT. Of the 405 pts with NHL, 64% had diffuse large B-cell, 19% had follicular, and %17%% had other histologic subtypes of lymphoma. Autologous peripheral stem cells were initially mobilized with either GCSF alone (n=331), VP-16 plus GCSF (n=141), or cyclophophamide plus GCSF (n=2). Poor harvests required additional attempts with VP-16 and/or cyclophosphamide plus GCSF (n=52). With a median follow-up of surviving patients of 52 months, 18 pts developed MDS/AML confirmed by morphology and/or clonal cytogenetics for an actuarial incidence of 7.9% at 7 years, with a crude rate of 3.4%. Pre-transplant characteristics including age, diagnosis of NHL or HD, bone marrow involvement, prior XRT, previous exposure to chemotherapy, LDH at the time of ASCT, disease status, and method of stem cell mobilization were then analyzed with respect to the subsequent development of MDS/AML. Five univariable risk factors for MDS/AML were identified using Cox analysis: previous exposure to XRT (HR=4.26, P=0.003), 4 or more courses of chemotherapy (HR=5.81, P=0.002), prior fludarabine exposure (HR=4.35, P =0.005), CD34+ cell dose <2.5X106/kg (HR=3.19, P=0.022), and 8 or more days of pheresis needed to harvest enough stem cells (HR=7.74, P<0.001). By multivariable analysis, previous exposure to XRT (HR=3.60, P=0.008), 4 or more courses of chemotherapy (HR=5.61, P=0.003), and 8 or more days of pheresis needed to harvest enough stem cells (HR=7.24, P<0.001) were identified as independent risk factors for MDS/AML. We conclude that pts who need 8 or more days of pheresis to harvest enough stem cells for ASCT have an increased risk of MDS/AML.

1/7/93
DIALOG(R)File 5:Biosis Previews(R)

0014793942 BIOSIS NO.: 200400161283
G-CSF-stimulated granulocyte transfusions from unrelated community donors for severe infections during neutropenia: A phase II multicenter trial of feasibility and efficacy.
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ABSTRACT: Granulocyte transfusions (GTx) are a logical approach for the treatment of serious infections that occur during chemotherapy-induced neutropenia. We examined the feasibility of a blood bank GTx program utilizing predominantly community donors who were stimulated with a single-dose regimen of G-CSF with or without oral dexamethasone. GTx recipients had severe bacterial or fungal infections, were neutropenic after systemic chemotherapy, and received GTx that were ABO/Rh and cytomegalovirus (CMV) compatible in addition to standard antimicrobial therapy. GTx were scheduled by protocol to be given each day until spontaneous recovery (ANC >1000); primary endpoint was % of days that GTx were provided when scheduled (success rate) in order to assess the feasibility of the approach. 40 patients (median age 46 yr, range 2-75) were enrolled from five oncology centers with mould infection (n=26), invasive bacterial infection (n=11), refractory bacteremia (n=9) and/or candidemia (n=2) (n>40 due to multiple infections in some patients). Underlying conditions included acute leukemia in 23 (58%) and stem cell transplant (SCT) in 15 (38%). Of the 351 days that granulocytes were indicated by protocol, 329 GTx were administered (93% success rate; mean, 8.2 GTx/patient). Success rate was similar among CMV seronegative patients (n=15, 92% success rate) and seropositive patients (93% success rate). Survival with complete or partial responses at 4 weeks after enrollment varied by infection type (4/26 (15%) for mould, 3/11 (27%) for bacteremia/candidemia, 4/11 (36%) for invasive bacterial infection) and by receipt of SCT (for mould, 2/9 (22%) among SCT recipients vs. 2/%17% (12%) for recipients of chemotherapy without SCT). Adverse events (AEs) were frequent in this severely ill population (median 2 AEs/patient, range 0-11), though only two serious adverse events (2 cases of transfusion-associated lung injury that resolved after discontinuation of GTx) were deemed related to the GTx. This multicenter study establishes the feasibility of daily GTx therapy from community donors for serious infections during neutropenia; providing CMV negative GTx to seronegative patients was feasible as well. Given the poor outcomes associated with serious infections during neutropenia and the uncertain efficacy and documented toxicity of GTx, a randomized trial of GTx plus antimicrobial therapy vs. antimicrobial therapy alone is urgently needed.

1/7/94
DIALOG(R)File 5:Biosis Previews(R)

0014793905 BIOSIS NO.: 200400161246
Allogeneic G-CSF stimulated bone marrow transplantation: Results of the harvest, engraftment and acute GVHD.
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ABSTRACT: It is well established that G-CSF - mobilized peripheral blood progenitor cells (PBPC) harvests contain more CD34+ cells and patients achieve a more rapid engraftment. Some reports, however, have indicated that the risk of developing chronic GVHD is higher, possibly because such PBPC harvests contain approximately 10 fold more T lymphocytes than bone marrow (BM) harvests. A few groups are trying to associate the faster engraftment of PBPC to the lower incidence of GVHD observed in BMT, using G-CSF - primed BM conventionally harvested from iliac crests for allo BMT. Between January 2001 and March 2003, 38 patients underwent sibling matched BMT with G-CSF - stimulated BM cells. After signing an informed consent form, all donors received subcutaneous G-CSF 5 mg/kg/day for 5 days (D-4 to D0). GVHD prophylaxis included cyclosporin from D-1 and methotrexate 15mg/m2 on D1 and 10mg/m2 on days 3, 6 and 11. Mycophenolate Mofetil (MMF) 15mg/kg/day was administered in 16 of 38 patients. Patients received G-CSF 10mg/ kg/day until hematological recovery. They were F:12; M:26; CML - 16, SAA - 9, AML - 5, ALL - 5, MDS - 2, NPH - 1. Median age was 30 (3-53 years). The BM harvests contained a median of 3.8X106 CD34+ cells per kg (range, 0.94-13.5X106/kg), 31X106 lymphocytes CD3+/kg (range 19-62.8 cellsX106/kg) and 12.9X106 lymphocytes CD8+/kg (range 8-30.2X106/kg). Median time to engraftment was 12 days (range, 6-20 days) to neutrophil and 21 days (10-%28%) to platelets. One patient experienced engraftment failure probably due to immunological rejection (multiple previous blood transfusions, including her parents) and other died before engraftment due to veno-occlusive disease. Acute GVHD grade gtoreqII occurred in 13 of 36 patients (36%) and grades III and IV occurred in 4 of 36 (11.1%). Comparing these results with data in literature we found that the median time to neutrophil engraftment in our study was much faster than unstimulated BM. Time to platelet engraftment, however, was similar to those observed in unstimulated BM harvests. CD34+ cell counts were between those found in non-stimulated BM and PBPC harvests. CD3+ and CD8+ counts were similar to those observed in conventional BMT. Apparently MMF did not delay engraftment. This approach allows the harvesting of high counts of CD34+ cells, what can be especially useful to promote faster engraftment in non-myeloablative BMT, without an increased incidence of acute GVHD. In 3 previous reports in the literature the incidence of chronic GVHD is lower when comparing to PBPC transplants.

1/7/95
DIALOG(R)File 5:Biosis Previews(R)

0014793888 BIOSIS NO.: 200400161229
Ex vivo expanded bone marrow combined with sub-therapeutic dose of peripheral blood progenitor cells after high-dose chemotherapy in poor mobilizers.
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LANGUAGE: English

ABSTRACT: A substantial number (nb) of candidates for high-dose therapy (HDT) fail to mobilize an adequate quantity of peripheral blood progenitor cells (PBPC) due to prior treatments (ttt) or to disease-related factors. Patients (pts) in whom 3 consecutive cytapheresis failed to collect gtoreq2.0X106 CD34+ cells/kg were considered poor mobilizers and were included in this study. We explored the feasibility of transplanting these pts after HDT with a sub-therapeutic dose of PBPC combined with a small volume bone marrow (BM) expanded ex vivo in the AastromReplicellTM Cell Production System.

Six pts from 3 centers with relapsing non-Hodgkin lymphoma (NHL) (n=4); multiple myeloma (n=1); or T-cell NHL (n=1) with prior long-lasting refractory anemia were included. Median (med.) age was 58.5 years (range 53-63). Med. nb. of previous lines of ttt was 2 (1-4). Mobilization consisted of chemotherapy (CT)+G-CSF (n=4), G-CSF alone (n=1), or in G-CSF following a 1st mobilization failure with CT+G-CSF (n=1). A med. nb. of 1.25X106 CD34+ cells/kg (0.89-1.8) were collected after 3 (n=5) or 2 (n=1) consecutive cytapheresis. Within 21 days (d.) after last cytapheresis, a med. of 3 ml/kg (2.3-5.3) BM was collected and inoculated in the bioreactor for a 12 d. ex vivo expansion. Pts received BEAM (n=5) or Melphalan 200 (n=1). Low dose PBPC were infused 48 hours after HDT followed within 6 hours by the expanded BM. Before expansion, BM contained a med. of 1.02X109 total MNC (0.5-1.2), 0.71X105/kg LIN-/CD34+ (0.5-8), 0.1X105 CFU-GM/kg (0.06-0.3) and 28X103 total CFU-F (12-1100). Final product expansion contained a med. of 2.0X109 total MNC (0.88-3.5), 0.52X105/kg LIN-/CD34+ (0.02-7.9), 0.06X105 CFU-GM/kg (0.03-0.3) and 213X103 total CFU-F (%17%-52200). We observed a med. 2.5 (1.3-3.2) and 5.8 (1.4-47.5) fold expansion of MNC and CFU-F respectively (resp.) in the expanded BM, without significant expansion of either CFU-GM or LIN-/CD34+. No acute toxicity were observed during infusion of expanded cells. Med. time to achieve an absolute neutrophil count >0.5X109/L and >1.0X109/L was resp. 11.5 d. (10-%28%) and 16.5 d. (12-42). Med. time to achieve an untransfused platelet count >20X109/L and >50X109/L was resp. 20 d. (10-76) and 30 d. (14-76+). The med. nb. of red cell and platelet transfusions was resp. 4 (0-NR) and 6 (5-20) but pt with prior refractory anemia remained dependant of red cell transfusions. Pts developed grade 2 (n=2) or 3 (n=4) infectious toxicity, and grade 4 mucositis (n=1). No other grade 3/4 toxicity was observed. All pts show a durable hematopoietic engraftment after a med. follow-up of 225 d. (85-414). This study demonstrates that addition of small volume ex vivo expanded BM to low dose PBPC is feasible and may allow successful hematopoietic recovery in poor mobilizers who could not have received otherwise HDT. The analysis of the expanded BM suggest that the expansion of stromal progenitor cells as measured by CFU-F might have a primordial role in the hematopoietic engraftment.

1/7/96
DIALOG(R)File 5:Biosis Previews(R)

0014793874 BIOSIS NO.: 200400161215
Analysis of CD34 subsets of patients undergoing autologous stem cell transplant (ABMT) with cells mobilized by either G-CSF alone or G-CSF plus VP-16.
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ABSTRACT: Mobilization of peripheral blood progenitor cells (PBPC) may be achieved with growth factors with or without chemotherapy. The combination of VP-16 plus G-CSF has previously shown to result in excellent PBPC yield. However, after prompt initial engraftment, we have observed a secondary platelet nadir, occurring several weeks post transplant, in some patients undergoing ABMT. We hypothesized that mobilization with G-CSF+VP-16 might contain fewer primitive CD34+ cell subsets than G-CSF alone. This analysis represents a retrospective review of 201 consecutive ABMT recipients undergoing transplant from 4/2000 to 5/2003. Median age was 52; primary diagnoses included NHL (59%), Hodgkin's disease (%17%%), multiple myeloma (%17%%) and other (7%). 27% had prior radiation therapy, 89% had chemosensitive disease at the time of transplant. 70 patients received G-CSF 10 mcg/kg/d alone for mobilization. 131 received VP-16 (2 gm/m2) plus G-CSF. This is a non-randomized study; pts receiving VP-16 were more likely to have NHL (76% vs. 27%) and less likely to have myeloma (3% vs. 44%). Patients receiving VP-16 mobilized significantly more total CD34+ cells (9.36 versus 5.76X106/kg, p<0.001). Patients receiving VP-16 collected more CD34+CD33- cells (12.3 vs. 5.3X106/kg, p<0.001) and CD34+CD61+ cells (3.5 vs. 1.8X106/kg, p<0.001). Both groups mobilized similar numbers of the most immature CD34+ cells, specifically CD34+CD38- (0.03 vs. 0.03X106/kg, p=0.97), CD34+DR- (0.09 vs. 0.07X106/kg, p=20), and CD34+CD33- (0.83 vs. 0.54X106/kg, p=0.%17%). These results suggest that the main difference between the two mobilization regimens is the number of committed progenitor cells. The minimum number of CD34+ cells infused for transplantation was 2.0X106/kg. Platelet engraftment was achieved in 14 days in each group; neutrophil engraftment occurred in 10 days in each group. The platelet count 6 weeks post transplant was also similar in both groups (median count 114X103/muL for VP-16 vs. 126X103/muL for G-CSF). The number of platelet transfusions was similar in both groups. While initial engraftment correlated with total CD34+ dose, as well as CD34+DR-, CD34+CD33+, CD34+CD61-, and CD34+CD61+ dose, the platelet count 6 weeks post transplant correlated only with CD34+DR- cells infused (p<0.001). We conclude that VP-16 plus G-CSF yields more committed CD34+ progenitors than does G-CSF alone. More primitive CD34 cells, as determined by the number of CD34+DR- cells, correlate with later sustained platelet engraftment.

1/7/97
DIALOG(R)File 5:Biosis Previews(R)

0014793865 BIOSIS NO.: 200400161206
A phase II study of stem cell mobilization with IV melphalan (60 mg/M2)+G-CSF in multiple myeloma.
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ABSTRACT: The optimal method for stem cell mobilization in myeloma patients has not been defined, but it should combine tumor-reduction with collection of 4 to 10 million CD34+ cells per kg, limited toxicity and minimal clonotypic contamination. Since intravenous melphalan (MEL) is the most effective agent for treating myeloma, we decided to examine MEL 60mg/m2X1 and G-CSF (10ug/kg/d) for mobilization. Over the past 3 years we have treated 32 patients (18M, 14W, median 57 years old, range 33-73) on a phase II trial, monitoring adequacy of CD34+ cell collection, tolerability, response of myeloma, and amount of clonotypic contamination assessed by patient-specific limiting dilution PCR (LD-PCR). Patients with chemoresponsive myeloma (>50% reduction in M protein), <3000 cGy prior radiotherapy, <200 mg prior oral melphalan, and Itoreq3 months of completing initial therapy, were eligible. Twenty-eight of 32 patients

(87.5%) achieved the target of 4X106 CD34+ cells/kg in ltoreq5 leukaphereses. Of the 4 who failed to achieve the target, 1 had a sixth leukapheresis and 2 were collected later with G-CSF alone; these 3 subsequently underwent stem cell transplant (SCT). Univariate analysis, using factors known to affect stem cell collection such as prior radiotherapy, and prognostic factors such as beta-2 microglobulin and CRP, showed that patients who failed to achieve the collection target had significantly higher CRP levels than patients who succeeded (p=.0212). The median numbers of days until leukapheresis (which began when WBC >5000/uL), CD34+ cells/kg collected and total leukaphereses were 16 days (12-30), 12.1X106 CD34+ cells/kg (2.6-52.8) and 2 leukaphereses (1-5). Febrile neutropenia during mobilization resulted in hospitalization in 12/32 patients (38%). Median days of grades 3 or 4 neutropenia and thrombocytopenia were 7 (2-20) and 8 (3-%17%). With respect to myeloma response, >50% reductions in disease were confirmed in 11 patients (34%) with 3 achieving a complete response (9%). Fifteen patients (47%) maintained prior responses, 5 had progressive disease (16%) and 1 was lost to follow up. Clonotypic myeloma cell contamination by LD-PCR was minimal (Blood 2003:102:477-9). Thirty patients have undergone SCT with no treatment-related deaths or significant complications, having received a median of 6.0 million CD34+ cells/kg. Hematologic recoveries were brisk and currently the median WBC, hemoglobin and platelet counts are 5,600/uL (3,100-10,800), 12.5g/dL (8.4-15.3) and 214,000/uL (98,000-324,000). Median event-free and overall survivals have not been reached. MEL 60+G-CSF for stem cell mobilization is feasible but requires transfusion support, usually results in collections sufficient for 2-3 autologous SCT with trace amounts of clonotypic contamination, and provides myeloma reduction or control in almost 90% of patients. Its impact on remission duration, long-term hematopoiesis and overall survival would best be studied in a randomized prospective clinical trial.

1/7/98
DIALOG(R)File 5:Biosis Previews(R)

0014793859 BIOSIS NO.: 200400161200
High efficiency mobilization of progenitor cells in myeloma using cyclophosphamide 2g/m2 with high-dose G-CSF.
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ABSTRACT: Although high-dose chemotherapy with peripheral blood stem cell support is now a standard of care for patients with myeloma, there is still no consensus about an optimal mobilization regimen. Many published studies and ongoing clinical trials use a mobilization protocol combining cyclophosphamide in doses ranging from 4-7g/m2 with G-CSF at a standard dose of 5mug/kg. We performed a retrospective single-centre audit of two consecutive patient cohorts, the first of which received intermediate-dose cyclophosphamide (IDC) (4g/m2) and standard-dose G-CSF (5mug/kg) (n=22), and the second of which received low-dose cyclophosphamide (LDC) (2g/m2) and 'high-dose' G-CSF (10mug/kg)(n=23). In both cohorts, G-CSF commenced 24 hours after completion of cyclophosphamide, and was continued until last day of harvest. All patients had received 3-6 cycles of conventional anthracycline/dexamethasone induction chemotherapy without prior exposure to alkylating agents. Patient groups were comparable with respect to age, Durie-Salmon stage at diagnosis, and response to chemotherapy. A successful collection was defined by a minimum harvest yield of gtoreq4.5X106 CD34+ cells/kg, sufficient to allow two cycles of high-dose therapy. The median Day 1 yields in the IDC and LDC groups were 3.25 (range 0.9-36.6) and 6.2 (2.2-12.5)X106 CD34+ cells/kg respectively. A Day 1 yield of gtoreq2X106 CD34+ cells/kg was achieved in 16 (73%) patients in the IDC group and in all 23 (100%) patients in the LDC group. A Day 1 yield of gtoreq4.5X106CD34+ cells/kg was achieved in 7 (32%) of the IDC group and %17% (74%) of the LDC group (p<0.05). The target yield of gtoreq4.5X106 CD34+ cells/kg was attained after a median of 2 days leucapheresis in 14 (64%) of the IDC group and after a median of 1 day leucapheresis in 21 (91%) of the LDC group. Fever (temperature over 38+-C) developed in 7 (32%) of the IDC group and 3 (13%) of the LDC group. Intravenous antibiotics were required in 8 (36%) of the IDC group and 3 (13%) of the LDC group. Of note, comparison of mobilization parameters revealed that the median circulating CD34+ cell count on Day 1 of harvest was twice as high (102.4/mul vs. 45/mul) in the LDC group, even though the corresponding white cell count was lower (8.8 vs. 13.4X109/L), suggesting that 'high-dose' G-CSF (10mug/kg) after chemotherapy may show different mobilization kinetics. Median number of days to first leucapheresis in the IDC group was 12 (range 10-%17%), compared to 9 (7-10 days) in the LDC group. Of interest for patient scheduling, 21 of 23 patients in the LDC group commenced leucapheresis within a two-day period (days 8,9) compared to only 14 of 22 patients (days 11,12) in the IDC group. Only 9 of 22 patients (41%) in the IDC group had a successful collection in a single leucapheresis session, compared to 18 of 23 patients (78%) in the LDC group (p<0.05). In summary, lower-dose cyclophosphamide (2g/m2) combined with 'high-dose' G-CSF (10mug/kg) appears to offer superior mobilization efficiency in the context of a primary therapy program for myeloma. This regimen is highly predictable and resource-efficient, is associated with less toxicity, and may be delivered in an outpatient setting.

1/7/99
DIALOG(R)File 5:Biosis Previews(R)

0014793856 BIOSIS NO.: 200400161197
Hematopoietic progenitor/stem cell mobilization after prior autologous blood and marrow transplant (BMT).
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ABSTRACT: Tandem autologous BMT (autoBMT) has been shown in randomized trials to provide survival in myeloma patients superior to that of a single transplant. However, many patients who have previously undergone a single autoBMT no longer have cryopreserved cells remaining in storage. For these patients, it is important to know if it is possible to collect further cells for use in BMT long after the original procedure. We have analyzed data from 34 patients (10 female/24 male) undergoing attempted remobilization at various timepoints following either a single or tandem transplant (median 4y; range 1-11y). In some cases remobilization was atttempted more than once (median 1; range 1-4). In those cases where remobilization was attempted more than once, there were different mobilization regimens used: G-CSF alone, G-CSF + GM-CSF, G-CSF+GM-CSF+Epo, and chemotherapy (cyclophosphamide alone or with etoposide, or the combination regimen DT-PACE) plus single or combined growth factors. Large volume leukapheresis on a Cobe Spectra was

initiated based on peripheral blood CD34 counts. The number of days of collection ranged from 2-10 (median 5). There were a total of 41 attempted collections: 8 yielded <2X10e6 CD34+ cells/kg; 9 yielded 2-5X10e6 CD34+ cells/kg; %17% yielded 5-10X10e6 CD34+ cells/kg; and 7 yielded >10X10e6 CD34+ cells/kg. A platelet count <125X10e9/L at the start of mobilization was generally associated with a poor yield, while a platelet count >200X10e9/L was generally but not invariably associated with a good yield. As %28% patients collected >2.5X10e6 CD34+ cells/kg and 24 of these had >4X10e6 CD34+ cells/kg. which are adequate and good grafts for autoBMT, respectively, we believe the option of recollecting cells should be explored for those myeloma patients in need of a second autoBMT but without cryopreserved cells already in storage.

1/7/100
DIALOG(R)File 5:Biosis Previews(R)

0014793855 BIOSIS NO.: 200400161196
Peripheral blood stem cell (PBSC) from HIV-positive patients (pts) with lymphoma have normal proliferative capacity and allow prompt and sustained hematopoietic recovery after myeloablative treatment.
AUTHOR: Re Alessandro (Reprint); Lanfranchi Arnalda; Ferremi Piero; Cattaneo Chiara (Reprint); Michieli Mariagrazia; Mazzuccato Maurizio; Casari Salvatore; Spina Michele; Carosi GianPiero; Tirelli Umberto; Rossi Giuseppe (Reprint)
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JOURNAL: Blood 102 (11): p953a-954a November 16, 2003 2003
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ABSTRACT: Hematopoietic stem cells are widely used to support high dose therapy (HDT) in HIV-negative pts with hematologic malignancies or solid tumours. These cells can be collected from peripheral blood in the vast majority of HIV-negative pts and allow long term engraftment after myeloablative treatment. The high incidence of hematopoietic failure in HIV infected subjects and the reduced in vitro proliferative potential of precursor cells from AIDS individuals create concern about the feasibility of these procedures in HIV-positive pts. We report our experience on 15 pts with refractory or relapsed HIV-related lymphoma enrolled in a multiinstitutional program of HDT and PBSC transplantation. All patients had received at least one line of intensive combination chemotherapy. Seven had HD and 8 had NHL; 87% had advanced stage (III-IV) and 3 had bone marrow involved. Median age was 39 (31-56). Median CD4 count was 183/cmm (%17%-506) and 5 pts had detectable HIV viremia; all pts received HAART throughout treatment and procedures. Twelve pts (80%) successfully collected a median of 6.8 (4.1-8.3)X106/Kg CD34+ cells after a median of 2 (2-3) apheresis; 6 pts after mobilization with Cyclophosphamide 4 gr/sqm + G-CSF 10 mcg/sqm and 6 at recovery after G-CSF-supported standard-dose chemotherapy (MINE in 4, ESHAP in 1 and MACOP-B in 1). Three patients failed mobilization after either G-CSF-supported chemotherapy (ESHAP in 2 and MINE in 1) and Cyclophosphamide+G-CSF. A total of 29 apheretic products were collected containing a median of 28X109 nucleated cells (10-92) and 187X106 CD34+ cells (53-394). The contents in progenitor cells of apheretic products, evaluated as Colony-Forming Units/105 cells, were comparable to what is seen in our laboratory in HIV-negative pts with lymphoma. The median number of CFU-GM, BFU-E and CFU-GEMM/105 cells was respectively 276 (108-1916), 282 (96-1983) and 7 (0-137). No detrimental effect was seen on progenitor cells after uncontrolled-rate freezing; the absolute recovery in CFU-GM, BFU-E and CFU-GEMM/105 cells after thawing was respectively 348 (49-452) (P=0.67), 284 (80-920) (P=0.53) and 6 (0-20) (P=0.53). Eleven pts actually received PBSC transplantation after BEAM conditioning regimen. Hematologic recovery was prompt in all pts (PMN>500/cmm at day +10 (8-10) and self-supporting plts >20.000/cmm at day +13 (8-18)). No graft failure were seen after a median follow-up of 8 months (4-21). In conclusion, PBSC with adequate contents in CD34+ cells can be collected in most HIV-positive pts even though with advanced lymphoma and heavy pretreatment. These cells have normal in vitro proliferative capacity and allow prompt and sustained hematopoietic recovery after myeloablative treatment.

1/7/101
DIALOG(R)File 5:Biosis Previews(R)

0014793852 BIOSIS NO.: 200400161193
Peripheral blood stem cell (PBSC) mobilization with high-dose vs. low-dose G-CSF: Analysis of a case control series.
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JOURNAL: Blood 102 (11): p953a November 16, 2003 2003
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LANGUAGE: English

ABSTRACT: Objective: PBSC mobilization typically requires administration of multiple daily doses of G-CSF to achieve target collections of CD34+ cells. A decrease in patient visits to the clinic may result in reduced overall costs and improved patient convenience. We report the effect of high-dose G-CSF on CD34+ cell yields, days to engraftment and number of apheresis collections for autologous stem cell transplants (SCT) as compared with a historical control. Methods: Fifty-eight collections for various malignancies occurred during 2001 (n=31) and 2002 (n=27). During 2001, G-CSF (10mcg/kg/day) was administered for five days followed by apheresis beginning on the sixth day. In 2002, 20mcg/kg/day of G-CSF was administered for two days followed by apheresis beginning on the third day. The target CD34+ count was 5X106 cells/kg (Coulter flow method) and no chemotherapy was used for mobilization. Results: The mean number of CD34+ cells collected was 5.66X106/kg (range 4.%17%-9.24) in 2001 compared to 8.39X106/kg (range 4.16-25.05) in 2002 (p=0.036). All patients achieved target CD34+ yields and less aphereses were required in the high dose (n=49) vs. the low dose (n=70) groups. Twenty-one patients received 22 SCTs in 2001 vs. 19 SCTs in 18 patients in 2002. There was no difference between the two groups in terms of mean days to myeloid engraftment (11.8 in 2001; 11.7 in 2002 (p=0.74)) or mean days to platelet engraftment (22.9 in 2001; 20.2 in 2002 (p=0.51)). In addition, actual drug costs per patient were decreased from apprxdollar sign2600 to apprxdollar sign2100. Finally, no difference in adverse effects was noted between the two groups. Conclusion: The results of our trial conclude that 20mcg/kg/dayX2 days vs. 10mcg/kg/dayX5 days of G-CSF results in improved CD34+ yield, decreased aphereses, and equivalent time to engraftment. This resulted in decreased patient travel and clinic time as well as slightly reduced drug costs.

1/7/102
DIALOG(R)File 5:Biosis Previews(R)

0014793851 BIOSIS NO.: 200400161192
Addition of rituximab to mobilization and preparative regimens successfully purges CD20 NHL and results in durable engraftment after autologous PBSCT.
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ABSTRACT: Immunotherapy plus high-dose chemotherapy with hematopoietic stem cell (PBSC) support expands cytotoxic potential by exploiting potential synergism of this unique combination and encompassing an in vivo purge of malignant tumor cells. In this study, the role of the anti-CD20 antibody rituximab, in combination with high-dose chemotherapy, was assessed in terms of safety and tolerability, CD20 depletion in leukapheresis products and CD20 recovery post-transplant, and mobilization of PBSC and engraftment after autologous PBSCT for NHL. The study design had two phases. In phase A, patients in first sensitive relapse received two doses of rituximab (375 mg/m2 on days -36 and -29) followed by cyclophosphamide (4 g/m2 on day -%28%). G-CSF mobilized PBSC (minimum 2.0X106 CD34+/kg) were initially collected when the WBC reached 1000/mul, but PBSC numbers improved when collection began with WBC>5000/mul. In phase B, patients received rituximab (375 mg/m2 on day -8) followed by high-dose cyclophosphamide (7.2 g/m2 total), VP16 (1.6 g/m2 total), and BCNU (450 mg/m2 total) (days -7 to -3). PBSC were infused on day 0. B and T cell subsets and IgS were monitored pre-transplant and on days 100, 180, 270, and 360 post-transplant. Twenty-two patients (11 males, 11 females; median age 52) were enrolled. All had intermediate grade CD20+ NHL (including 13 diffuse large cell, 3 transformed large cell, 3 mantle cell with two in leukemic phase). Nine had marrow involvement with NHL at diagnosis and two at relapse. The median number of chemotherapy regimens was two and 11 patients had received prior rituximab. Rituximab in combination with high-dose chemotherapy was well tolerated. Nineteen of 22 patients mobilized with the aid of G-CSF alone. The median number of leukaphereses was 1.5 (range, 1-6), and 10 patients collected in one pheresis. The median MNCX108/kg was 1.4 (range, 0.1-5.1) and median CD34X106/kg was 3.0 (range, 2.1-6.6). One patient required G-CSF plus GM-CSF to collect PBSC and two others required marrow harvest. All patients engrafted successfully. The median days to ANC >500/mul was 11 (range, 8-13) and to platelets >20,000/mul was 14 (range, 10-19) after PBSC infusion. By day 180, neutrophil engraftment was complete in all patients (n=19), and by day 360, only one (n=12) had persistent thrombocytopenia (platelet count 35,000/mul). Of 54 apheresis products, the median % positivity of CD3 was 11.3 and of CD19 was 0 (range, 0-3.1). B cell recovery significantly improved after six months post-BMT. CD19 counts pre and at +100, +180, +270, and +360 were 1, 2.5, 6, 98, and 149 cells/mm3, respectively. CD20 counts pre and at +100, +180, +270, and +360 were 1, 1, 9, 94, and 148 cells/mm3, respectively. CD4:CD8 ratios pre and at +100, +180, +270, and +360 were 0.4, 0.5, 0.5, 0.5, and 0.5, respectively. The median follow-up of survivors is 19 months (range, 4-26). Six of 22 have relapsed and one developed AML post-PBSCT. Four have died 2-15 months post-PBSCT (3 from NHL, one AML). In conclusion, PBSC can be mobilized and result in durable hematopoietic engraftment after rituximab and with chemotherapy and growth factor support. The timing of PBSC collection may be improved with recovery of WBC to >5000/mul and with the aid of peripheral CD34 assessment. While initial response for the combination of rituximab and high-dose chemotherapy is favorable, longer follow-up is required to determine impact on PFS and OS.

1/7/103
DIALOG(R)File 5:Biosis Previews(R)

0014793803 BIOSIS NO.: 200400161144
In-vivo engraftment and multi-lineage differentiation of human embryonic stem cell (hESC)-derived hematopoietic cells in primary fetal sheep recipients.
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LANGUAGE: English

ABSTRACT: We used transplantation into 1degree and 2degree pre-immune fetal sheep recipients (55-62 days-old, term: 145 days) to evaluate the in vivo potential of hematopoietic elements derived from hESC. The in utero human/sheep xenograft model has proven valuable in assessing the in vivo hematopoietic activity of stem cells from a variety of fetal and post-natal human sources. Two transplant groups with cells from differentiated hESC (H1 and H1.1) were established. Human ESCs were differentiated on mouse S17 cell line for %17% days. The %17%-day cultures were found to be positive for CD34, CD133, CD38, Gly-A, CD33, CD15, CD10, and CD56. Each fetus (n=7) in group 1 was transplanted with 0.75-2.8X105 CD34+/CD38- cells isolated from the day %17% cultures by FACS sorting, while each fetus in group 2 (n=13) was given 0.13-0.95X105 CD34+/Lin- cells obtained similarly from the day %17% cultures. The animals were allowed to complete gestation and be born. Three recipients (2 in group 1 and 1 in group 2) were lost to study (fetus absorbed). Four animals in group 1 and 5 animals in group 2 were found to be chimeric with a variety of donor (human) cell types which in some cases have persisted for 13 months post-transplant. For example, the relative percentages of human cells expressing CD34, CD45, CD3, CD13, CD133, CD38, HLA-DR, and CD2 at 5 months post-transplant for an animal in group 1 were: 0.05, 0.26, 0.20, 0.10, 0.15, 0.09, 4.4, and 0.04, while at 3 months post-transplant the values for cells expressing CD45, CD3, CD133, CD38, HLA-DR, and Gly-A for an animal in group 2 were: 0.5, 0.6, 0.4, 0.3, 0.6, and 0.5 respectively. The donor (human) cells appear to be responsive to human cytokines. The administration of human G-CSF to group 1 animals on two separate occasions at 4 and 12 months post-transplant resulted in increased donor cell activity. Increases in human cell activity were also noted in chimeric animals in both groups treated with human GM-CSF. Examination of 4 animals from both groups sacrificed at intervals after birth failed to reveal any gross anatomical abnormalities; all live sheep appear to be healthy. Evaluation at 2 months post transplant of one 2degree recipient transplanted with 2X104 CD34+ cells isolated from bone marrow of a group 1 primary recipient, or of three 2degree recipients each transplanted with 0.5X106 CD45+ cells obtained from bone marrow of the same primary donor failed to reveal human cell activity. Finally, we have examined livers from sacrificed 1degree recipients and found significant numbers of donor (human) derived hepatocytes. We have also found human cardiomyocytes and Purkinje fibers in sheep heart. These findings indicate that hESCs are capable of generating hematopoietic cells that engraft and undergo long-term, multi-lineage differentiation in the 1degree sheep recipients. The initial serial transfer studies suggest that the cells used for transplantation may not fulfill the criteria for long-term engrafting hematopoietic stem cells in this model. Perhaps a variation in the technique for deriving hematopoietic elements from hESCs for transplantation may be warranted.

1/7/104
DIALOG(R)File 5:Biosis Previews(R)

0014793757 BIOSIS NO.: 200400161098
Either IL-12 or interferon-gamma can correct the dendritic cell defect induced by TGFbeta1 in patients with myeloma.
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ABSTRACT: The poor response to immunotherapy in patients with multiple myeloma indicates that a better understanding of the defects in the immune response in this disease is required before effective immunotherapy strategies can be developed. Recently we reported that high potency (CMRF44+) dendritic cells (DC) in the peripheral blood of patients with multiple myeloma failed to upregulate the expression of the B7 costimulatory molecules, CD80 and CD86, in response to an appropriate signal from trimeric soluble CD40 ligand (huCD40LT). During antigen presentation to T cells the level of expression of the B7 molecules provides an important "second signal" that determines the fate of each cell - apoptosis, anergy or productive immunity. We have previously demonstrated that this defect is caused by TGFbeta1 and IL-10 produced by malignant plasma cells and that it is possible to neutralise the defect in vitro with anti-TGFbeta1 (Blood 98:2992). If this defect has an impact on immunotherapy strategies, it would be important to identify another agent with a similar biological effect as anti-TGFbeta1, which could be used in vivo. The number of high potency DC (CMRF44+, CD14-, CD19-, PI-) in the blood of patients with myeloma (0.03-0.8% of mononuclear cells; n=26) was not significantly different from normal controls (0.05-0.8% of MNCs; n=13). The expression of the costimulatory molecules CD80 and CD86 on the blood DC of these patients (29+-%17%% and 85+-10% of MNCs respectively) was also normal (29+-%17%% and 86+-16% of MNCs). Incubation with huCD40LT stimulated upregulation of CD80 expression on the DC and B cells of normal controls but there was either reduced or no upregulation of CD80 on the DC of the patients with myeloma. Less than 10% of malignant plasma cells expressed CD80 and huCD40LT failed to significantly upregulate CD80 expression on mature plasma cells (n=6). Upregulation of CD80 on DC of normal controls was inhibited by rTGF-beta1 in a dose dependent manner. CD86 expression on DC was high both before (86%) and after (89%) stimulation. Either IL-12 or interferon-gamma could replace anti-TGFbeta1 as an agent capable of neutralising the failure to stimulate CD80 upregulation by huCD40LT. DC stimulated by IL-12 were predominately myeloid DC (CD11c+ and CDw123-) which are known to initiate a Th1 type response whereas DC in G-CSF apheresis harvests had an increase in lymphoid DC suggesting that these cells might initiate a Th2 response. Patients with CD80 deficient DC tended to have a lower number of circulating Th2 cells as determined by a flow cytometric assay for intracellular cytokine expression (n=13). Thus patients with myeloma have a normal number of DC but may fail to upregulate CD80 expression in the presence of huCD40LT or other agents due to tumour-derived TGF-beta1 and/or IL-10. This DC defect can be corrected with either IL-12 or interferon-gamma to provide a Th1 response.

1/7/105

0014793682 BIOSIS NO.: 200400161023
Phase I/II trial of adding semi-synthetic homoharringtonine (HHT, Myelostat(R)) in CML patients who have achieved complete cytogenetic response on imatinib.
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ABSTRACT: Imatinib mesylate induces complete cytogenetic responses (CCyR) in a high proportion of patients with CML in chronic phase, but evidence of leukemia at low level is still detectable by RT-PCR in the majority of such responders. Homoharringtonine (HHT) is an alkaloid that binds to ribosomal peptidyl transferase, thus blocking the translation phase of protein synthesis and leading to apoptosis. HHT has been studied extensively in CML patients and is synergistic when combined with imatinib in vitro. We designed a phase I/II trial in which semi-synthetic homoharringtonine (Myelostat(R)) was added in patients who had reached CCyR on imatinib but whose level of BCR-ABL transcripts appeared to have reached a plateau. Inclusion criteria: Patients had to satisfy all the following criteria: (1) A CCyR on imatinib, (2) A plateau in the BCR-ABL/ABL ratio defined as three consecutive samples over a minimum of six months after achieving CCyR that showed a variation of less than 20% from the peak value, (3) An ANC >1.5X109/l and platelet count >150X109/l unsupported, and (4) Imatinib administered at a dose of 400 or 600/mg day unchanged during the previous 6 months. Protocol: HHT was given at a dose of 2.5mg/m2 in two divided daily doses subcutaneously for 1 day (dose level I) together with the imatinib (400 or 600 mg/day). Oral granisetron (2 mg) was also given at the time of the HHT administration. Courses were repeated every %28% days. The dose of HHT was escalated by adding one day of treatment every two courses (eg dose level II: 2.5mg/m2X2 days; dose level III: 2.5mg/m2X3 days, etc) Patients were taught to self-administer the drug. G-CSF was given in order to maintain the ANC >1.0. Patients were monitored by RT-PCR at the beginning of each course. Results: So far nine patients have been enrolled. Four patients were taking imatinib at 600 mg/day and five at 400mg/day. Five have completed treatment at dose level I and three at dose level II. Five patients had grade I lethargy on the days of administration. Nausea was not observed. Four patients suffered local irritation at the injection site which resolved rapidly. One patient received G-CSF during courses at dose levels I and II. No other hematologic toxicity has so far been observed. Imatinib was not discontinued or its dose reduced in any patient. The RT-PCR analysis after completion of dose level I showed a modest reduction in transcript numbers in all the 8 patients. Two of the three patients who have completed treatment at dose level II had a reduction in BCR-ABL transcript numbers of more than one log (1.04 log and 1.0 log respectively) compared with starting values; both patients were taking 600 mg of imatinib. We conclude that HHT at the dose levels employed can safely be combined with imatinib and may contribute to an overall reduction in the total number of leukemia cells in a patient's body.

1/7/106

0014781789 BIOSIS NO.: 200400148450
Engraftment of SCID-repopulating cells is independent of VLA-4 and mediated by VLA-5 after short-term expansion culture.
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ABSTRACT: The pivotal role of VLA-4 in mediating hematopoietic stem cell (HSC) lodgment in the bone marrow (BM) is well documented while the importance of VLA-5 appears to be less significant. Several studies indicate that ex vivo cytokine stimulation induces defective HSC engraftment. We used NOD/SCID b 2m null mice repopulating cell (SRC) assays to compare the activity of VLA-4 and VLA-5 integrins in engraftment of unmanipulated and cytokine-treated human cord blood (CB) HSC. Recipient mice were transplanted with 150-200X103 freshly isolated CB CD34+ cells or their expansion product following 3 days of serum-free culture supplemented with SCF, IL, TPO, IL-6 and G-CSF. Integrin function was assessed by incubating grafts with neutralizing antibodies P4C2 (anti VLA-4) or P1D6 (anti VLA-5) prior to infusion. Control cells were treated with anti-CD34 antibody. Human chimerism in recipient BM was determined by flow cytometric detection of human CD45+ cells. Co-expression of CD19 or CD33 was used to evaluate multilineage repopulation. After transplantation of uncultured control CD34+ cells, human chimerism was 37.6+-11.4% CD45+ cells. VLA-4 neutralization resulted in decreased engraftment (1.6+-0.9% CD45+ cells, P<0.05), while VLA-5 neutralization had no significant effect (22.9+-9.9% chimerism). After expansion culture, BM repopulation by control cells was at 36.3+-9.3%. Prior incubation of expanded cells with anti VLA-4 did not affect SRC activity (48.9+-7.4% chimerism) whereas VLA-5 neutralization reduced engraftment down to 2.7+-1.1% CD45+ cells (P<0.05). All mice were reconstituted with lymphoid and myeloid cells in similar ratios, indicating that VLA-4 and VLA-5 blocking antibodies did not target populations of committed progenitors but rather inhibited engraftment of multilineage reconstituting cells. When direct homing of CD34+ cells in the recipient mice BM was determined at 20 hours after transplant, similar changes in integrin activity were detected. BM homing of uncultured CD34+ cells (control value: 0.98+-0.09% of infused cells) was significantly inhibited by VLA-4 neutralisation (0.06+-0.01%, P<0.05) while VLA-5 neutralisation had no such effect (1.10+-0.%17%%). On the contrary, homing of expanded CD34+ cells (control value: 0.75+-0.19%) was not significantly affected by blocking VLA-4 (0.42+-0.03%) but was markedly reduced after incubation with VLA-5 blocking antibody (0.15+-0.04%, P<0.05). In conclusion, while homing and engraftment of native human SRC are VLA-4 dependent, ex vivo expansion is associated with VLA-4 inactivation which uncovers the role of VLA-5 in mediating in vivo hematopoietic reconstitution.

1/7/107
DIALOG(R)File 5:Biosis Previews(R)

0014781758 BIOSIS NO.: 200400148419
Phosphatidylinositol 3-kinase is constitutively activated and involved in the growth signaling in primary Ph-negative acute myeloid leukemia cells.
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ABSTRACT: Recently, it was found that Akt, a crucial substrate of phosphatidylinositol 3-kinase (PI3-kinase) is constitutively phosphorylated and activated in acute myeloid leukemia (AML) cells and that Akt is involved in the survival of AML cells. Although Akt is mainly phosphorylated and activated by the PI3-kinase-dependent mechanism, PI3-kinase activity in primary AML cells has not yet been analyzed. Moreover, the PI3-kinase-independent mechanism of Akt activation in leukemia cells is not yet fully understood. In the present study, to examine the activation of PI3-kinase in the leukemia cells from 24 patients with Philadelphia-negative AML (M0, 2; M1, 3; M2, 7; M3, 2; M4, 3, M5, 4; M6, 2; M7, 1), we performed an in vitro PI3-kinase assay using anti-phosphotyrosine immunoprecipitates from lysates of AML cells after obtaining informed consent from the patients. PI3-kinase was constitutively activated in 14 (58.3%) of 24 AML cases. Constitutively activated PI3-kinase was detected in 8 (80%) of 10 AML cases whose leukemia cells spontaneously proliferated in the absence of cytokines. In contrast, PI3-kinase is constitutively activated in 6 (42.9%) of 14 cases whose leukemia cells proliferated only after stimulation with cytokines (G-CSF, GM-CSF, SCF and TPO). P85alpha, a regulatory subunit of PI3-kinase, was expressed in all of the 24 cases in the present study. 3H-thymidine incorporation assay revealed that the selective PI3-kinase inhibitor LY294002 dose-dependently inhibited the spontaneous proliferation of AML cells. IC50s were 1-5 muM. The proliferation of AML cells induced by cytokines (G-CSF, GM-CSF, SCF and TPO) was also dose-dependently inhibited by LY294002 (IC50s; 1-5 muM). We next analyzed the phosphorylation of Akt on Ser473 and Thr308 by Western blotting using phospho-specific antibodies. Constitutive phosphorylation of Akt was detected in 11 (64.7%) of %17% cases analyzed, including 7 cases in which PI3-kinase was not constitutively activated. The incidence of Akt phosphorylation in AML cells is higher than that of PI3-kinase activation. Interestingly, Akt was constitutively phosphorylated on Ser473 and Thr308 in one case with M1, in which constitutive activation of PI3-kinase was not detected. These findings strongly suggest that the PI3-kinase-Akt pathway plays a crucial role in the proliferation of AML cells and that the PI3-kinase-independent pathway is involved in Akt activation in AML cells, at least in part.

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DIALOG(R)File 5:Biosis Previews(R)

0014781398 BIOSIS NO.: 200400148059
Long-term outcome of autologous transplantation of peripheral blood progenitor cells for patients 60 years of age and older with acute myelogenous leukemia in first complete remission.
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JOURNAL: Blood 102 (11): p741a November 16, 2003 2003
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ABSTRACT: The optimal post-remission treatment for elderly patients with AML is presently unknown. Recent studies have reported the feasibility of autologous stem cell transplantation in this population. To better understand the long-term outcome of autologous transplantation in older patients, we evaluated high-dose chemoradiotherapy preparative conditioning followed by peripheral blood progenitor cell (PBPC) transplantation as post-remission therapy in 27 patients age 60-71 y

(median 65 years) with newly diagnosed AML in first complete remission. Pretreatment characteristics included male gender (18 patients, 66%), antecedent hematologic disease (8 patients, 29%), and adverse cytogenetics (5 patients, 9%). All patients had achieved complete remission using standard induction chemotherapy. Patients then received a single cycle of consolidation therapy with cytarabine (2gm/m2 q12hX8 doses), mitoxantrone (10mg/m2/day X3), and G-CSF (5mg/kg/day IV starting one day after consolidation until completion of progenitor cell collection). Eleven patients gtoreq also received IL-2 (3X106 IU/m2 SQ b.i.d. X10d) starting when the recovering ANC post-consolidation reached 1000mm-3. A median of four collections were required to procure a minimum of 1X106 CD34+ cells/kg. Cytogenetic analysis of the PBPC product was performed using standard techniques. PBPCs were infused one day after preparative conditioning with TBI (1125 cGy in 5 fractions) and cyclophosphamide (60mg/kg/day X2). No post-transplant G-CSF was given, however, 11 patients received IL-2 administered following neutrophil recovery at the same dose and schedule as after consolidation. Successful engraftment occurred in 26 patients (96%). The median number of days to ANC >500 mm-3 and platelets >20,000 mm-3 was 16 days (range 11 to 36 days) and 20 days (range 3 to 60 days), respectively. Median follow-up from CR for the entire group was 11 months (range 5.9 to 93.0 months). Transplant-related complications included paroxysmal atrial-fibrillation in two patients (7%), hepatic veno-occlusive disease in one patient (4%), pneumonia in one patient (4%), and Sweet's syndrome in one patient (4%). Median LFS and overall survival are 9.6 months (range 3.3 to 83.9 months) and 10.9 months (range 3.9 to 102.1 months), respectively. Actuarial leukemia-free survival and overall survival at three years are %28%%+-9% and 25%+-9%, respectively. Seven are alive in continuous CR while 19 died from relapse and one died from pneumonia. Our results show that autologous transplantation of PBPC procured after a single cycle of cytarabine-based consolidation chemotherapy is well-tolerated and feasible for patients older than 60 years of age with AML in first CR. Future investigation should focus on evaluating a larger group of elderly patients in first CR and comparing autologous stem cell transplantation with conventional cytarabine consolidation chemotherapy in randomized studies to identify optimal post-remission therapy.

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DIALOG(R)File 5:Biosis Previews(R)

0014781397 BIOSIS NO.: 200400148058
Addition of anti-CD33 purged autologous peripheral blood stem cells to purged marrow speeds time to engraftment compared with purged autologous marrow alone for acute myelogenous leukemia.
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ABSTRACT: Previous studies have demonstrated that residual leukemic cells contaminate most acute myeloid leukemia (AML) autografts and contribute to relapsed disease. Non-randomized studies using purged-bone marrow (BM) autografts in AML have demonstrated that purging of residual leukemia cells is feasible but leads to significantly delayed neutrophil and platelet engraftment compared with unpurged autologous BM transplantation. This delay increases the risks of transplantation. We undertook a study to determine if antibody-purged BM and PBSC in combination would lead to shorter time to hematologic engraftment. From September 1995-August 2000, eleven patients with AML (8 in CR2; 2 in CR1 who had been refractory to primary induction, and 1 in PR with skin involvement but no marrow involvement) were enrolled. Eligible patients needed to express >20% CD33+ cells by flow cytometry at diagnosis or relapse. All patients were in histologic remission at the time of enrollment as defined by <5% blasts in the marrow. Patients underwent a bone marrow harvest and then received mobilization chemotherapy with cytarabine or cytarabine and daunorubicin followed by G-CSF and stem cell collection. Purging of BM and PBSC was achieved using a murine anti-CD33 antibody, MY9 in conjunction with rabbit complement. Conditioning at the time of transplant was cyclophosphamide 60 mg/kg/d for 2 days and 1400 cGy TBI. Median age was 52 (range 20-65), 10 of 11 patients engrafted neutrophils (defined as ANC >500/mul) and 9/11 engrafted platelets (defined as a platelet count >20,000/mul for four weeks without platelet transfusion). One patient in PR died of sepsis and relapsed disease prior to engraftment, while the other patient died of a motor vehicle accident on day +427. Median time to neutrophil and platelet engraftment using combined purged PBSC and BM was %17%.5 days (range 14-547 days) and 24 days (range 15-639 days), respectively. These results compare favorably to a cohort of 30 patients treated at our institution who had received anti-CD33-purged BM alone (median time to neutrophil engraftment of 41 days (range 18-59 days); p=0.01 and platelet engraftment 56 days (range 16-279 days); p=0.04). At 2 years post transplant, overall survival and disease-free survival are 45%+-15% (mean+-SE). With a median follow-up of 59 months, 6 patients have relapsed and died, 1 has died without recurrence and 4 are living at 56+, 58+, 59+ and 62+ months after transplant. There was one transplant related death in a patient who developed pseudomonal sepsis. This study demonstrates that the strategy of antibody-purged PBSC has favorable results in terms of engraftment and overall survival. This makes feasible a comparison of purged versus unpurged autologous PBSC transplant for AML with little transplant related mortality.

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DIALOG(R)File 5:Biosis Previews(R)

0014781390 BIOSIS NO.: 200400148051
The value of autologous PSCT versus autologous BMT for patients with AML in first CR and impact of mobilized numbers CD34-cells on outcome: Final results of the randomized AML-10 trial of the EORTC LG and GIMEMA.
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ABSTRACT: In the AML 10 trial, patients (pts) achieving CR after one or two induction courses with either daunorubicin, mitoxantrone or idarubicin combined with cytarabine and etoposide in a 3+10+5 regimen, received one consolidation course with high dose cytarabine and the same anthracycline as during induction. Pts with an HLA-identical sibling donor had to receive an allogeneic BMT, otherwise an autologous SCT had to be performed. In an amendment to the trial pts without a donor received lenograstim (G-CSF) from day 20 of the consolidation course to mobilize peripheral stem cells (PSC), followed by randomization between BMT and PSCT. A total of 292 pts aged between 16 and 60 years have been randomized: 146 for BMT, and 146 for PSCT. The BM harvest was successful in 97 (66%) of the pts in the BMT arm. The mobilization was adequate in 112 (77%) of the pts in the PSCT arm; 21 pts in the PSCT arm required

more mobilization rounds to achieve an adequate harvest. In CR1 95 (65%) BMTs have been performed in the BMT arm and 103 (71%) PSCTs in the PSCT arm. 14 (10%) pts in the BMT arm received PSC and 5 (3%) patients in the PSC arm received BM. The hematological recovery was slower in the BMT arm: the median number of days to reach gtoreq20X109/l platelets was 77 in the BMT arm versus 23 in the PSCT arm (p<0.0001), the median number of days to reach gtoreq0.5X109/l neutrophils was 42 versus 22 days resp. (p<0.0001). This resulted in a higher number of transfusions: 8 versus 4 packs of RBC (p<0.0001) and 34 versus 14 packs of platelets (p<0.0001). The median number of days on intravenous antibiotics was 19 days in the BMT arm versus 11 days in the PSCT arm (p<0.0001). The median duration of hospitalization was 41 days and 24 days resp. (p<0.0001). The median follow-up was 4.5 years; 147 pts relapsed, 12 died in CR1, and overall 135 pts died. Based on an intent-to-treat analysis, the 5-year DFS rate was 47.5% (SE=4.3%) in the BMT arm vs 41.5% (SE=4.2%) in the PSCT arm (p=0.34; HR=1.%17%, 95% CI 0.85-1.59). The 5-year incidence of relapse was 47.6% in the BMT arm and 55.0% in the PSCT arm (p=0.24; HR=1.21, 95% CI 0.88-1.68). The 5-year incidence of death in CR was low in both arms: 4.9% in the BMT arm and 3.5% in the PSCT arm. The 5-year survival rates were 54.9% (SE=4.3%) vs 49.6% (SE=4.4%) respectively (p=0.57, HR=1.10, 95% CI 0.79-1.55). The highest yield of CD34-cells obtained in a single apheresis during the first round of mobilization had a very strong prognostic importance (p=0.0001): the 5-year DFS rate in pts with a high yield (gtoreq7X106/kg: n=61) was 18.6% (SE=6.0%) vs 50.1% (SE=5.4%) in those with medium yield (1-6.9X106/kg: n=87) vs 69.7% (SE=8.0%) in those with low yield (<1X106/kg: n=33) vs 53.6% (SE=7.0%) in those with no harvest (n=52). The impact of the CD34 yield on outcome was apparent in both the PSCT arm and the BMT arm. In conclusion: PSCT resulted in similar duration of survival as compared with autologous BMT, despite a slight increase in relapse risk after APSCT. The hematopoietic recovery was substantially faster after APSCT. This resulted in lower requirement of transfusions and antibiotics and in a 2-week shorter hospitalization. The highest number of CD34-cells obtained during the first round of mobilization is a strong prognostic factor, independently of cytogenetic features (p=0.002).

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DIALOG(R)File 5:Biosis Previews(R)

0014781293 BIOSIS NO.: 200400147954
Sirolimus, tacrolimus and low dose methotrexate as graft versus host disease prophylaxis after matched related and unrelated nonmyeloablative transplantation is well tolerated and associated with a low incidence of acute GVHD.
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ABSTRACT: The promise of reduced regimen related toxicity associated with nonmyeloablative stem cell transplantation (NST) has been achieved through the use of lower doses of chemotherapy and/or radiation; however, complications from acute graft versus host disease (GVHD) have prevented the benefits of NST from being fully realized. Sirolimus (rapamycin) is a macrocyclic lactone similar in structure to tacrolimus and cyclosporine but with a distinct mechanism of action. Sirolimus binds to both FKBP12 and mTOR and inhibits signal transduction and cell cycle progression. The drug is synergistic with tacrolimus but has a distinct toxicity profile, thereby allowing their use in combination. We report results of a phase II trial combining sirolimus with tacrolimus and low-dose methotrexate (MTX) as GVHD prophylaxis in matched related and unrelated donor NST. Eligible patients were not candidates for myeloablative transplantation due to advanced age, prior transplant or other medical conditions. All patients received fludarabine (30 mg/m2/dX4days) and intravenous bususlfan (0.8mg/kg/dX4 days) as conditioning. GVHD prophylaxis included Sirolimus 12 mg loading dose on day -3 and then 4 mg po qd targeting a serum level of 3-12 ng/ml. Tacrolimus was initiated at 0.05 mg/kg po b.i.d. beginning day -3 with a targeted serum level of 5-10 ng/ml. MTX (5 mg/m2) was given days, 1, 3 and 6. Planned taper of the GVHD medications was apprx30% at days 60, and 120 with discontinuation by day 180. All patients received G-CSF mobilized peripheral blood stem cells with a targeted cell dose of 1X107 CD34+ cells/kg. Patients received G-CSF 5 mcg/kg beginning day 1. The median follow up is 6 months and all evaluable patients have been followed for >100 days. 25 patients have been enrolled, 14 with related and 11 with unrelated donors. The median age was 55 years (range 20-69). Diseases included: 5 Hodgkin's disease, 3 AML, 6 CLL, 4 MDS, 3 CML, 2 NHL, 1 MM and 1 CMML. 12 patients (48%) had received prior myeloablative transplantation. %17% patients (68%) had active disease at the time of transplantation. Sirolimus was well tolerated and no adverse events related to the drug were noted. Only, 40% of patients developed a nadir ANC <500 and neutrophil recovery was prompt. One patient died early after transplantation of progressive disease and was not evaluable for GVHD. Only 2 of 24 evaluable patients (8%) developed acute GVHD (both grade II skin). Both patients received grafts from unrelated donors. 6 patients have relapsed. 23 of 25 patients were evaluable for donor chimerism between day 30 and 45 after transplantation. The median level of donor derived hematopoiesis in bone marrow was high, 92% (range 13% to 100%). Only 4 patients had less than 60% donor derived hematopoiesis by day 45. This included 3 patients with advanced stage CLL and 1 patient with CMML who had minimal engraftment of donor cells (13%) and eventual autologous reconstitution. The addition of sirolimus to tacrolimus and low dose MTX is well tolerated and associated with a low incidence of acute GVHD. This regimen is also associated with a high level of donor hematopoietic chimerism. With further patient accrual and longer follow-up, information on the incidence of chronic GVHD and overall outcome will be available.

1/7/112
DIALOG(R)File 5:Biosis Previews(R)

0014781280 BIOSIS NO.: 200400147941
Predictive factors for hematopoietic engraftment after autologous peripheral blood stem cell (PBSC) transplantation for treatment of AL amyloidosis.
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RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: AL amyloidosis is caused by a plasma cell dyscrasia in which clonal immunoglobulin light chains deposited in tissues leads to organ failure and death. Treatment with high dose melphalan and autologous PBSC rescue produces hematologic remissions in approximately 40% of evaluable patients and improvements in organ disease and quality of life. However, these patients, who frequently have amyloid deposits in bone marrow blood vessels and interstitium and impaired function of kidneys, liver, spleen,

and heart, represent an unusual population for stem cell transplantation, with unique problems. To identify factors influencing engraftment rates after infusion of autologous G-CSF-mobilized PBSCs, we studied a group of 257 AL patients. The median time to neutrophil engraftment (neutrophil count greater than 500X106/L) was 10 days (range, 8-%17% days). In a multivariate analysis, the factors positively affecting neutrophil engraftment were CD34+ cell dose gtoreq3.5X106/kg (hazard ratio (HR)=1.72, 95% confidence interval (CI)=1.27-2.34), female gender (HR=1.53, 95% CI=1.18-1.99), and minimal prior alkylator therapy (cumulative melphalan dose ltoreq100 mg, HR=1.49, 95% CI=1.04-2.%17%). The median time to platelet engraftment (untransfused platelet count greater than 20X109/L) was 13 days (range, 7-63 days). For platelet engraftment, in addition to CD34+ cell dose gtoreq3.5X106/kg (HR=1.88, 95% CI=1.38-2.56), positive factors included preserved renal function (for proteinuria ltoreq5 g/day, HR=1.38, 95% CI=1.06-1.78; for serum creatinine level ltoreq1.2 mg/dl, HR=1.80, 95% CI=1.24-2.61) and the absence of neutropenic fever (HR=1.4, 95% CI=1.08-1.82). The dose of intravenous melphalan was not found to be an independent predictive factor for hematopoietic recovery. Thus, in this unique patient population, organ function as well as hematopoietic factors influence engraftment after PBSC rescue.

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DIALOG(R)File 5:Biosis Previews(R)

0014781242 BIOSIS NO.: 200400147903
Impact of VLA-5 expression on the reconstitution properties of hematopoietic stem cells mobilized by cyclophosphamide/G-CSF.
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ABSTRACT: Mobilized peripheral blood has replaced bone marrow as the preferred source of stem/progenitor cells in transplantation settings because of its reported accelerated promotion of hematopoietic reconstitution. The intruiging question how the contrasting processess of mobilization and homing/engraftment are interconnected remains largely unanswered. In this study, we first analyzed the expression of adhesion molecules on hematopoietic stem cell subsets in normal bone marrow (NBM) and bone marrow (MBM) and peripheral blood (MPB) after mobilization and tested their migratory behaviour towards SDF-1. Splenectomized CBA/H mice were mobilized by a combined cyclophosphamide/G-CSF protocol. The most striking observation was that in the Lin- fraction the number of VLA-5 expressing cells decreased from 79+-3% in NBM to %17%+-3% in MPB. Furthermore, it was determined that these MPB cells showed enhanced migration towards SDF-1 compared to NBM and MBM, which was accompanied by a further decrease to 3+-2% of VLA-5 expressing cells in the migrated fraction (M-MPB). Since VLA-5 has been implicated in the adhesive interactions of stem cells with the bone marrow extracellular matrix and stromal cells, we unexpectedly found an inverse relationship between hematopoietic reconstitution and the percentage VLA-5 expressing cells following transplantation of equal number of progenitor cells. M-MBP cells (low expression) demonstrated a much faster hematopoietic recovery than MPB cells (intermediate expression) followed by the NBM/MBM cells (high expression). Next, we investigated whether differences in homing potential of the stem cell subsets might be responsible for these observations. Three hours after transplantation no differences in homing efficiency of progenitor cells from MPB and MBM could be detected (13+-1% vs 13+-3% in the bone marrow, and 12+-2% vs 16+-3% in the spleen of the recipients). Although stem cells (CAFC-%28%) homed with a higher efficiency, again no differences between MPB and MBM could be observed (21+-3% vs 24+-1% in the bone marrow, and 12+-1% vs 15+-1% in the spleen of the recipients). However, the homing efficiency of MPB-progenitor cells slightly increased to 18+-5% in the bone marrow at twenty-four hours after transplantation while that of MBM-progenitor cells was decreased to 8+-3%. In the spleen no differences in homing efficiencies could be detected at this time point between MPB and MBM progenitor cells (8+-0.4% vs 7+-2%, respectively). Finally, the grafts were labelled with PKH67-GL and the number of VLA-5 expressing cells in the Lin-PKH+-fraction of the bone marrow and spleen of the recipients determined. At three hours after transplantation of MPB cells a rapid increase from %17%+-3% to 58+-10% of VLA-5 expressing cells was observed in the bone marrow of the recipient. This level increased up to 90+-6% at twenty-four hours after transplantation. In the spleen of the recipients these values were 40+-8% and 34+-2%, respectively. In the case of MBM-grafts the percentage of VLA-5 expressing cells in the spleen of the recipient decreased from 82+-6% to 61+-7% at three hours post-transplant and remained lower (64+-18%) up to twenty-four hours post-transplant. In conclusion, it is demonstrated that MPB cells show little VLA-5 expression but these cells have an enhanced hematopoietic reconstitution potential. A rapid upregulation of VLA-5 expression on MPB engrafting cells to ensure adhesion and subsequent hematopoietic reconstitution is occuring early after transplantation and during the initial phase of homing in the bone marrow.

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DIALOG(R)File 5:Biosis Previews(R)

0014781209 BIOSIS NO.: 200400147870
Etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) can cytoreduce resistant myeloma patients and mobilise them for transplant without adverse effects.
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Up to 30% of patients with myeloma respond poorly to first-line therapy with VAD-type regimens, but many remain candidates for high dose therapy. We studied the efficacy of the ESHAP regimen (etoposide 40mg/m2/d, d1-4; methylprednisolone 500mg/day, d1-5; cisplatin 25mg/m2/d continuous iv infusion, d1-4; cytarabine 2g/m2, d1; G-CSF, 10 mg/kg/d from d6-16) as second-line therapy in 42 patients with newly diagnosed stage II or III myeloma (median age 50.5, range 31-68 y), who had failed VAD-type therapy (disease status by EBMT criteria after primary therapy: 9 PR, 12 MR, 19 NC and 2 PD). The rationale for using ESHAP was to improve disease response and act as a mobilisation regimen to procure stem cells where possible, and the study included 6 patients with PR after primary therapy who received ESHAP due to persistently heavy BM infiltration with plasma cells (median 38%, range 20-79%). Of 21 patients with NC or PD after VAD-type therapy, 14 (67%) responded (7 converting to PR, 7 to MR). Of 12 patients with MR after VAD-type therapy, 7 (58%) converted to PR, 4 showed NC and 1 had PD after ESHAP. Data regarding BM plasma cell (BMPC) infiltration at diagnosis, after VAD-type therapy and after ESHAP are available in 26 patients, showing median BMPC at

diagnosis of 52% (range 10-100%), after first line therapy of 23.5% (range 5-100%), and after ESHAP of 15% (range 0-80%). Overall, ESHAP was well tolerated. Thirty patients (71%) remained asymptomatic despite documented neutropenia in most, ranging from day 6-21 after ESHAP. Twelve patients were readmitted with complications following ESHAP: 7 with neutropenic sepsis (all responded to broad-spectrum intravenous antibiotics), 1 with a perforated bowel, 2 with nausea and vomiting, 1 with presumed Pneumocystis pneumonia and 1 with Hickman line-related endocarditis. Renal function based on GFR measurements taken pre and post ESHAP deteriorated in 16 out of 25 patients. Median reduction in GFR values was 21.5% (range 7-79%), but in 9 of these, GFR remained normal (>70ml/min). Of the remainder, all but 1 patient had normal serum creatinine levels following ESHAP. Thirty-two patients underwent PBSC mobilisation with ESHAP/G-CSF and 9 with cyclophosphamide/G-CSF. In ESHAP-mobilised patients, median CD34+ yield was 7.3X106/kg (range 0.4-43.8X106/kg; 87% achieved >2X106/kg). Thirty-eight patients proceeded to high dose therapy (26 had 1 autologous PBSCT, 2 had 2 non-tandem autologous PBSCT, 3 had low-intensity allograft, 4 autologous PBSCT followed by low-intensity allograft and 3 had myeloablative allograft), after a median of 2 months without an increase in infective complications, renal toxicity or in-patient stay compared to similar patients who had not received ESHAP. In 2 of these, follow up is too short for assessment. In the remaining, median follow up following initial treatment with ESHAP is %28%.8 months (range 4.5 to 68.8 months): 8 are in CR, 13 in PR, 7 are receiving further salvage therapy for PD and 8 have died of PD. Our results indicate that ESHAP has acceptable toxicity, useful cytoreductive potential and efficient PBSC mobilising capability in patients with sub-optimal responses to first line therapy. In particular, this non-cross reactive regimen achieved a significant degree of reduction in BM plasmacytosis in this chemoresistant group of patients, and did not adversely affect transplant outcome.

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DIALOG(R)File 5:Biosis Previews(R)

0014780941 BIOSIS NO.: 200400147602
Two courses of high-dose araC/mitoxantrone (HAM) versus standard dose TAD followed by HAM for induction modifies the prognosis of AML patients in poor rather than good prognostic groups: An ongoing study by the German AMLCG.
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JOURNAL: Blood 102 (11): p618a November 16, 2003 2003
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ABSTRACT: Postremission high-dose vs intermediate or standard dose araC (Cancer Res 58:4173, 1998) and similarly autologous transplantation vs chemotherapy alone (Lancet 351:700, 1998; Best Practice and Research Clin. Haematol. 14:95, 2001) have been found to improve remission duration in favorable and not in unfavorable prognostic groups of patients with AML as defined by cytogenetics or cytogenetics combined with percentage of b.m. blasts after the 1st induction course, respectively. We are currently investigating dose effects of induction treatment on the outcome of patients in different prognostic groups according to multiple risk factors. Starting in June 1999 1094 patients 16-81 (median 60) years of age have been entering the trial and randomized to either HAM-HAM with high-dose araC 3(1 in gtoreq60 Y) g/m2X6 or TAD-HAM for induction. Both arms were balanced for age </gtoreq60 Y, diagnosis de novo/secondary AML and MDS, karyotype favorable/intermediate/unfavorable, and LDH ltoreq/>700 U. Furthermore, the two induction arms were balanced for the upfront randomized G-CSF priming yes or no, and for prolonged maintenance or autologous transplantation. Significant differences in the relapse-free survival (RFS) between the two induction regimens X and Y (blinded) are seen in older (p=.018) rather than younger patients, and those with high (p=.0033) rather than low LDH, while neither patients with favorable nor those with unfavorable karyotype contributing 10% and %17%% to the patients show these differences. Based on a multivariate analysis a combined poor risk group was defined including age 60+ Y or unfavorable karyotype or LDH >700 U or day 16 bone marrow blasts >40%, while in a combined good risk group documented absence of any of the poor risk features by complete data was required. In the combined poor risk group representing 69% of the patients induction X vs Y resulted in a superior RFS (p=.0024) while in the combined good risk group (29% patients) this difference in RFS is not seen. Similarly to RFS, differences in favor of induction X versus Y are found in the survival of patients entering and the survival of patients attaining CR in those of 60+ Y (p=.031/.034), patients with LDH >700 U (p=.0054/.039), and patients in the combined poor risk group (p=.0069/.03 8). Thus, considering multiple combined risk factors a poor rather than a good prognosis in AML may be modified by different intensity induction treatment.

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DIALOG(R)File 5:Biosis Previews(R)

0014780939 BIOSIS NO.: 200400147600
Treatment results of childhood acute myeloid leukemia.
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ABSTRACT: One hundred eighty-six children with acute myeloid leukemia (AML) were enrolled in the Taiwan Pediatric Oncology Group (TPOG) 97 AML protocols between Jan. 1, 1997 and May 31, 2002. Twenty-two with acute promyelocytic leukemia (APL) were treated with TPOG-APL-97 or TPOG-APL-2001 protocols. Non-APL patients were stratified to two different protocols based on different hospitals: 100 patients to a novel TPOG-AML-97A protocol, 64 to a modified MRC AML-10 protocol. The present study comprised the former 100 non-APL patients and 22 APL patients. There were 64 boys and 58 girls aged below 18 years. FAB subtypes included 8 patients with M0, 12 M1, 36 M2, 22 M3, 11 M4, 19 M5, 6 M6, and 7 M7. Genetic subtypes (by cytogenetics and/or molecular analyses) included 4 patients with inv(16), 19 t(15; %17%),9 MLL, 17t(8;21), 2 patients with monosomy 7, 5 patients with complex chromosomal abnormalities and 47 patients with normal karyotype or other changes. Three children were of Down syndrome. The TPOG-AML-97A protocol consisted of induction therapy with idarubicin 9 mg/m2/day, and Ara-C 100 mg/m2/day (3+7) q3w, post-remission therapy with four monthly courses of Ara-C 1 gm/m2q12hX8 plus etoposide 100 mg/m2/dayX5 alternated with Ara-C 1 gm/m2q12hX8 plus mitoxantrone 10 mg/m2/dayX4, and then four monthly

courses of idarubicin 9 mg/m2/day and Ara-C 200 mg/m2/day (1+5). The TPOG-APL-97 protocol consisted of induction therapy with ATRA 30 mg/m2/day and idarubicin plus Ara-C (same dosages and durations as TPOG-AML-97A) if WBC count increased, and post-remission therapy with six monthly courses of idarubicin and Ara-C (same dosages and durations as TPOG-AML-97A). The TPOG-APL-2001 protocol, followed TPOG-APL-97, consisted of induction therapy with ATRA plus idarubicin, consolidation therapy with 3 monthly courses of idarubicin 9 mg/m2/dX3, and then maintenance therapy including ATRA 15 days every 3 months, 6-MP and MTX for 2 years. Intrathecal MTX was given on the first day of chemotherapy containing idarubicin. Prophylactic G-CSF was used after intensive chemotherapy in post-remission stage. Twenty-two patients underwent BMT during post-remission stage based on the judgement of their physicians. The rate of achieving remission in non-APL patients was 89%, in APL 100%. Twenty-five patients with non-APL relapsed, 21 in bone marrow and 4 in bone marrow and CNS; 2 patients with APL relapsed, both in bone marrow. The 5-year overall EFS was 53.1% (95% CI, 44.3% to 63.5%). The 5-year EFS in MO was 30%, M1 54%, M2 50.6%, M3 78.8%, M4 50.9%, M5 50.1%, M6 75%, and M7 16.7%, in inv(16) 66.7%, t(15; %17%) 78.8%, MLL rearrangement 37%, t(8; 21) 57.5%, monosomy 7 and complex chromosomal abnormalities 53.6%, normal karyotype or other changes 45.1%, and Down syndrome 100%. The 5-year overall survival was 54.8% (95% CI, 45% to 66.8%). The 5-year EFS in patients treated with TPOG-AML-97A was 47.7% (95% CI, 38.2% to 59.5%). Univariate analysis on survivals revealed that those who attained complete remission after only one course of induction therapy had a significantly better EFS (78.3% vs 47.1%, p=0.006), whereas gender, age and WBC count had no impact on survivals. The disease-free survivals in BMT and chemotherapy patients were 59.6% and 60.9%, respectively (p=0.86).

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DIALOG(R)File 5:Biosis Previews(R)

0014780757 BIOSIS NO.: 200400147418
The role of beta-catenin in chronic myelogenous leukemic progenitor expansion.
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ABSTRACT: Beta-catenin, an important downstream regulator of Wnt signaling is frequently mutated in epithelial malignancies and plays a key role in hematopoietic stem cell self-renewal. However, the role of beta-catenin in the pathogenesis of myeloid leukemias such as chronic myelogenous leukemia (CML) has not been fully established. Although CML is believed to arise as a consequence of clonal expansion of defective primitive hematopoietic progenitors, the role of hematopoietic stem cell self-renewal genes, such as beta-catenin, in expansion of the leukemic stem cell pool has not been established. Also, the contribution of more committed myeloid progenitors to CML disease progression has not been fully examined. Previous studies with mouse transgenic models of myeloid leukemia, including blast crisis phase CML, revealed a marked expansion of myeloid progenitors that were enriched for leukemic stem cells (LSC). Similarly, five color FACS analysis of human CML bone marrow and peripheral blood samples demonstrated a marked expansion of myeloid progenitors in chronic phase (CP; n=%17%), accelerated phase (AP; n=22) and blast crisis (BC; n=11) compared with normal bone marrow or G-CSF mobilized peripheral blood (n=15). While CML CP was characterized by an expansion of megakaryocyte erythroid progenitors (MEP), AP was marked by a predominant common myeloid progenitor (CMP) population and BC by an increase in granuloctye macrophage progenitors (GMP). In order to determine whether beta-catenin, a critical regulator of HSC self-renewal and proliferation was aberrantly overexpressed in CML, we compared the expression of beta-catenin in normal and CP, AP and BC CML HSC and myeloid progenitors. Confocal fluorescence microscopy (Zeiss LSM), performed using an antibody directed at non-phosphorylated (activated form) beta-catenin, revealed increased nuclear beta-catenin expression in AP and BC CML compared with normal myeloid progenitors but was comparable between normal and CML HSC. Furthermore, FACS analysis demonstrated elevated intracellular beta-catenin expression in AP and BC CML compared with normal myeloid progenitors while beta-catenin expression was comparable in CML and normal HSC. Moreover, beta-catenin induced activation of stem cell self-renewal is mediated by intra-nuclear binding of beta-catenin to the transcription factors LEF and TCF. Thus, to assay binding of beta-catenin to LEF and TCF, normal and CML HSC and myeloid progenitors were transduced with a lentiviral LEF/TCF GFP vector containing the consensus binding motif for beta-catenin. Although normal (n=9) and CML (CP=2, AP=2, BC=5) HSC (34+38-90+Lin-) displayed similar LEF/TCF reporter GFP levels after 7 to 10 days in culture, CML myeloid progenitors (CD34+CD38+Lin-) demonstrated greater GFP expression than their normal counterparts indicative of increased nuclear translocation of beta-catenin. These data suggest that activation of the Wnt signaling pathway through over-expression of activated beta-catenin in myeloid progenitors may enhance their leukemic potential perhaps as a result of reacquisition of self-renewal capacity and higher proliferative capacity.

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DIALOG(R)File 5:Biosis Previews(R)

0014780752 BIOSIS NO.: 200400147413
Retroviral overexpression of human HoxB4 confers an ex vivo growth advantage to CD34+ cells from dogs, baboons, macaques and humans.
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ABSTRACT: Over-expression of the human HoxB4 gene has been shown to induce ex vivo expansion and self-renewal of murine long term repopulating multilineage hematopoietic stem cells. Successful ex vivo expansion of stem cells has great potential for clinical cell therapy applications. Since mouse and human differ substantially with respect to stem cell biology, we have started to develop a large animal model to study the effect of HoxB4 on hematopoietic stem cells in a clinically more relevant experimental setup. We investigated if human HoxB4 enhances in vitro expansion of CD34+ cells from mobilized dog peripheral blood (PB), cytokine primed baboon and macaque bone marrow (BM), human cord blood (CB) and mobilized human PB. Baboon, macaque and human cells were cultured in IMDM/10%FCS in the presence of human TPO, SCF, Flt3-L, IL-6, IL-3 and G-CSF each at 100 ng/ml. Dog cells were cultured in human Dexter media with Flt3-L, canine SCF and canine G-CSF, each at 50 ng/ml. Enriched CD34+ cells were pre-stimulated for 2 days and then transduced twice with Phoenix-GALV or RD114 pseudotyped MSCV-HoxB4-ires-GFP or the control vector, MSCV-ires-YFP. Cells were maintained in suspension cultures. Cultures were split every week, and flow-cytometric analysis for GFP/YFP-expression and CFU assays were performed. After 4 weeks

culture, the percentage of HoxB4-overexpressing dog cells increased from 30% to 76% (n=5), while YFP (mock)-transduced dog cells decreased from 53% to 30% (n=5) (p<0.05, paired T test). The same HoxB4-mediated growth advantage was observed for baboon (GFP from 29% to 63% and YFP from 33% to 26%)(n=4) (p<0.05) and macaque (GFP from 32% to 80% and YFP from 38% to 43%)(n=4) (p<0.05). In dog, macaque and baboon cells, HoxB4-overexpression resulted in an up to %28%-fold expansion of CFUs compared with YFP-transduced control cells. Transduction with the HoxB4-vector also augmented total cell expansion 3 to 5-fold in suspension cultures of dog, baboon and macaque cells when compared with YFP-transduced controls (p<0.05). In human CB, HoxB4 overexpression induced a 2-fold augmented expansion in the number of CFUs relative to YFP control. Of note, flow cytometric analysis of liquid cultures did not show a difference in human cord blood cells (GFP from 81% to 53% and YFP from 93% to 56%) (n=3). In preliminary experiments we were unable to demonstrate a HoxB4 mediated in vitro growth advantage in human PB CD34+ cells. In conclusion, our data demonstrate that HoxB4 has an effect on CD34+ cells from dog, macaque and baboon. The effect on human PB cells is less pronounced than that on human CB cells. Our data indicate that either of the two non-human primates or the canine model can be used to investigate the effects of HoxB4 on hematopoietic stem cells in a clinically relevant model.

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DIALOG(R)File 5:Biosis Previews(R)

0014780524 BIOSIS NO.: 200400147185
Long-term outcome of acquired aplastic anemia children treated with antithymocyte globulin, cyclosporine with or without G-CSF.
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ABSTRACT: BACGROUND: Acquired aplastic anemia (AA) is thought to be an immune-mediated disease. Immunosuppressive therapy (IST) has been the treatment of choice for patients who did not have suitable donors. Previously, we had published promising results of IST for children with acquired AA(Blood 2000; 96:2049). In the study, overall survival rate (OS) at 4 years was 83% in patients with vSAA and 92% in those with SAA/nonSAA. OBJECTIVES: Here we report follow-up results focusing on patients with relapse. PATIENTS and TREATMENT: From 1992 to 1997, 119 newly diagnosed children with acquired AA (median age 9) entered AA-92 study. 50 vSAA patients were treated with ATG+CyA+mPSL+danazole+G-CSF, 36 SAA and %28% nonSAA patients were treated with ATG+CyA+mPSL+danazole+/-G-CSF. Complete remission (CR) was defined as a neutrophil count >1.5X10-9/L, a platelet count >100X10-9/L, and a hemoblobin level of >11 g/dl. Partial response (PR) was defined as a neutrophil count >0.5X10-9/L, a platelet count >20X10-9/L, and a hemoglobin level of >8.0 g/dl. Relapse was indicated by the return of the PB counts to levels meeting the definition of SAA and/or the requirement for blood transfusion. Response rate was 71% at 6 months in vSAA patients, 65% in SAA/nonSAA patients, respectively. No patient responded after 6 months. Therefore, 75 responders and 29 non-responders at 6 months were analyzed their OS, relapse rate (RR), and treatment-failure-free survival (TFFS). The median observation time of surviving patients is 80 months, ranging from 44 to 130 months. RESULTS: Among 119 patients, 37 patients received BMT and %17% patients died during an observation period. The OS was 79.2+-6.7% at 9 years, but has not reached plateau. The RR was 27.7+-4.9%. There is no statistically significant difference in OS between the responders and non-responders (90.7+-3.4% vs. 55.1+-23%, p=0.09). Of the 75 responders, 22 patients relapsed and the RR was 30.5+-5.5% at 9 years. Fourteen patients received 2nd ATG therapy and 5 of them responded. Ten of the 22 patients with relapse received alternative donor BMT and 7 are alive. TFFS of the 75 was 67.3+-5.3%. OS after relapse was 75.9+-9.5%. New clonal abnormalities appeared in 9 of 119 patients (10.0+-3.2%KM probability): monosomy 7(3 patients), trisomy 8(3 patients), trisomy 9, trisomy11, del (13)(1 patient each). We did not observe any patients with clinical PNH. Among 65 surviving responders, 33(51%) have CR and 26(40%) PR at last follow-up time. CONCLUSIONS: Our data demonstrate that IST is effective for children with acquired AA, but relapse and secondly clonal disease are common. Effective 2nd line treatment should be developed.

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DIALOG(R)File 5:Biosis Previews(R)

0014780450 BIOSIS NO.: 200400147111
Reduced-intensity regimen for unrelated donor transplantation (UDT) as salvage therapy for prior recipients of autologous stem cell transplantation.
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ABSTRACT: From June 2000 to July 2003, 14 patients underwent reduced intensity unrelated donor transplants (UDT) after failing a previous autologous transplant for hematologic malignancies. Thirteen of the patients had relapsed with their original malignancy prior to the UDT. One patient had a therapy-related myelodysplasia (MDS) after undergoing an autologous transplant for Hodgkin lymphoma (HL). Six patients were females and 8 males, with a median age of 45 (range 18-61). Thirteen patients received an autologous transplant for the following diagnoses: myeloma (3), non-Hodgkin lymphoma (5), acute myeloid leukemia (AML) (3), Hodgkin lymphoma (2). One patient had a syngeneic transplantation for AML. For autologous stem cell mobilization, patients with lymphoma and myeloma received cyclophosphamide (CY) 4 g/m2 and G-CSF. Preparative regimens used for autologous transplantation: patients with lymphoma received combination of CY, VP-16 and BCNU; myeloma patients received busulfan (BU), CY and TBI and AML patients received BUCY. One patient with lymphoma was transplanted using a preparative regimen containing high-dose CY, VP-16 and 131I-tositumomab. The median time from first transplant to UDT was 26 months (range 9-87 months). The preparative regimen for UDT was fludarabine 25 mg/m2 (day -11 to -7), BU 0.5 mg/kg orally every 6 hours for 16 doses (day -6 to -3), mycophenolate 750-1,000 mg orally twice a day (day -6 to 0) and total lymphoid irradiation (TLI) of 4 Gy given on day 0. All patients received peripheral stem cell grafts. Thirteen patients received a fully matched graft (A, B and DR; DR loci defined by allele typing), one patient received a B-antigen mismatched graft. Graft-versus-host disease (GVHD) prophylaxis was a combination of tacrolimus (Tac) and methotrexate (MTX). Tac 0.06 mg/kg twice a day orally was started on day -6 and continued until day 56, tapered by 20% every 4 weeks thereafter and discontinued on day 180 if there was no GVHD. MTX 5 mg/m2 was given on days 1, 3, 6 and 11 following

transplantation. With a median follow up of 13 months, the Kaplan-Meier estimate of survival at 2 years was 44%+-%17%%. Bone marrow chimerism study obtained at day 30 showed complete donor chimerism in 11 patients. The remaining 3 patients converted to full chimerism by day 90. One patient had full chimerism at day 30 and converted to mixed chimerism at the time of relapse. Six patients died; four from progressive disease (2 Hodgkin lymphoma, 1 myeloma and 1 non-Hodgkin lymphoma), one each from GVHD and thrombotic thrombocytopenic purpura. One patient with myeloma developed multiple subcutaneous plasmacytomas 2 years after UDT. She was treated with donor lymphocyte infusions with resolution of the subcutaneous nodules. Five out of 14 patients developed grade III-IV acute GVHD; one patient died of GVHD. Two patients progressed to chronic GVHD and 4 additional patients developed de novo chronic GVHD. Of the 6 patients with chronic GVHD, 3 had limited and 3 had extensive disease. Adverse events associated with this regimen were mainly mild nausea and vomiting that were easily controlled with antiemetics. This reduced intensity regimen containing fludarabine, busulfan and TLI in UDT is an effective salvage therapy for patients who failed prior autologous transplantation for hematologic malignancy.

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DIALOG(R)File 5:Biosis Previews(R)

0014780443 BIOSIS NO.: 200400147104
Dose and timing of preemptive donor lymphocyte infusions after allogeneic CD34+selected blood stem cell transplantation from unrelated donors.
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ABSTRACT: Thirty three patients (median age 42, range 23-55) with high-risk hematologic malignancies (AML/MDS 14, ALL 9, CML 7 and MM 3) were treated according to a protocol utilizing transplantation of CD34+selected allogeneic stem cells and preemptive T-cell add-backs after myeloablative conditioning. All patients had high-risk disease either by unfavourable cytogenetics or failure of previous therapies. Conditioning was melphalan 140mg/m2, thiotepa 10mg/kg and cyclophosphamide 120mg/kg in 27 or total body irradiation (12Gy) and cyclophosphamide 120mg/kg in 6 patients. ATG (20mg/kg) was given to avoid graft rejection. Mobilized peripheral blood progenitor cells from matched unrelated donors (31) or HLA-identical siblings (2) were depleted of T-cells by CD34-selection with the Isolex 300i. Cyclosporine was given for additional GvHD prophylaxis. Patients received G-CSF (Filgrastim) to accelerate neutrophil recovery. In the first 10 patients two T-cell add-backs from the cryopreserved negative fraction of the selected apheresis product were scheduled for day 50 (0.5X106CD3/kg) and day 100 (1X106CD3/kg) in the absence of GvHD. Selected grafts contained a median of 4.20X106CD34+cells/kg (range 1.96-8.30) and 0.31X105CD3+cells/kg (range 0.03-5.90). Twenty eight of 29 patients surviving more than 30 days had engraftment of donor cells as confirmed by chimerism analysis (WBC >1000/ul on day 11, median, range 9-67, PLT >20000/ul on day 13, median, range 8-%28%). One patient who had not received ATG rejected but recovered hematopoiesis after infusion of autologous PBPCs. Among the first 10 patients 3 individuals with CML had early reappearance of Ph+ cells despite preemptive DLI requiring additional cell therapy in 2. As a consequence DLIs were given earlier in the following patients (day 25 and day 50) which prevented early cytogenetic relapse in the following patients with CML. Three patients (10%) developed aGvHD (2 grade I-II, 1 grade III-IV) spontaneously and 16 patients (67%) developed aGvHD after DLI (12 grade I-II, 4 III-IV). After a median follow up of 546 days (median, range 48-1520) 19 patients are alive (58%, 16 in CR, 2 in hematologic and 1 in molecular relapse). Eight of 24 evaluable patients developed chronic GvHD (33%, 6 limited, 2 extensive). Six patients died after relapse (18%) and 8 died from transplantation related causes (24%). Two of these died as a direct consequence of GvHD following preemptive DLI. Patients with myeloid malignancies had a better survival ($p<0.05$) than patients wit ALL or MM. We conclude that preemptive DLI from unrelated donors following CD34+selected stem cell transplantation after myeloablative conditioning can be performed without excessive toxicity. Lymphocyte infusions should be given early after transplantation as soon as the immediate toxicity of the conditioning regimen has resolved to avoid early relapse. While on therapeutic levels of cyclosporine A, CD3+cell doses between 0.5 and 1.0X106/kg are sufficient to induce effective graft versus leukemia reactions with a low risk of severe acute or chronic GvHD.

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DIALOG(R)File 5:Biosis Previews(R)

0014780438 BIOSIS NO.: 200400147099
Impact of transplant CD34+ cell dose on outcomes after allogeneic peripheral blood stem cell transplantation from a matched unrelated donor.
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ABSTRACT: There is accumulating evidence that transplant CD34+ cell dose influences outcomes after allogeneic hematopoietic stem cell transplant from a sibling donor. However, its impact on outcomes after peripheral blood stem cell transplant from a matched unrelated donor has not been well described. Therefore, we studied a cohort of 34 patients who underwent a G-CSF mobilized peripheral blood stem cell transplant from a matched unrelated donor in our institution and analyzed the impact of the graft CD34+ cell dose on engraftment and clinical outcomes. All patients gave written informed consent for City of Hope protocol 1089 approved by the local institutional review board. Patient age ranged from 16 to 68 (median 48). Twelve were female and 22 were male. The cohort consisted of 13 patients with AML, 6 with ALL, 5 with CML, 4 with NHL, and the remaining 6 with other diagnosis (CLL, MDS, MPD). Patients were conditioned with either a full-intensity regimen (n=20) or reduced-intensity regimen using fludarabine plus either melphalan or busulfan (n=14). Median (ranges) CD34+ cell and mononuclear cell doses were 7.1 (1.2-30.2)X106/kg and 786 (126-1860)X106/kg, respectively. All patients engrafted with the median time to ANC >500/uL at 15 days (range: 8-52) and platelet >20k/ul at 19 days (range:11-67). After a median follow up of 376 days (range: 100-1139), seventeen patients are alive. The actuarial probabilities of overall survival (OS), disease-free

survival (DFS), and relapse were 45% and 41%, and 31% respectively. The actuarial probability of grade 2-4 acute GVHD was 58% (grade 3-4: 48%). Five of %17% patients with a CD34+ cell dose <median required 3 weeks or longer to achieve ANC >500u/l compared with one of %17% with a CD34+ cell dose >median (p=0.04). The higher total mononuclear cell dose was associated with shorter days to achieve platelet transfusion independence post-transplant (p=0.006). There was no difference in overall acute GVHD between the two groups, but the higher CD34+ cell dose was associated with increased grade II-IV acute GVHD (p=0.03). In univariate analysis, the CD34 cell dose >median was not significantly associated with DFS, OS, or relapse rate. When the CD34+ cell dose was adjusted for conditioning regimen in a Cox multivariate model, there was a trend for better DFS, OS, and Time to relapse associated with higher CD34+ cell dose. In conclusion, our data suggest that there may exist a CD34+ cell dose effect on engraftment and clinical outcomes after peripheral blood stem cell transplant from a matched unrelated donor.

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DIALOG(R)File 5:Biosis Previews(R)

0014780371 BIOSIS NO.: 200400147032
Durable engraftment and long-term survival following fludarabine-based nonmyeloablative hematopoietic cell transplantation (HCT) in allo-immunized patients with ATG-refractory severe aplastic anemia (SAA) and paroxysmal nocturnal hemoglobinuria (PNH).
AUTHOR: Chakrabarti Sakti (Reprint); Takahashi Y (Reprint); Srinivasan R (Reprint); Marquesen M (Reprint); Shalabi R A (Reprint); Goodwin R (Reprint); Swanson P (Reprint); Espinoza-Delgado I; Bolan C D; Leitman S F; Barrett A J (Reprint); Young N S (Reprint); Childs R (Reprint)
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ABSTRACT: We evaluated the toxicity-profile, engraftment potential, and efficacy of nonmyeloablative allogeneic HCT using fludarbine-based conditioning in patients with either ATG refractory SAA (n=10) or severe PNH (n=4) associated with thrombosis and/or transfusion dependence. All patients enrolled on study were heavily transfused before transplantation including 6 who had HLA allo-antibodies and 2 patients with allo-antibodies to RBCs. Fourteen patients, median age 26.5 years (range %17%-44 years), received Fludarabine (25 mg/m2X5 days), ATG (40mg/kgX4 days) and Cyclophosphamide (60mg/kgX2 days) followed by infusion of an un-manipulated G-CSF mobilized allograft from an HLA matched sibling (n=10), parent (n=2), or single antigen mismatched sibling (n=2). GVHD prophylaxis consisted of Cyclosporine (CSA) either alone (n=2) or combined with Mycophenolate mofetil (n=10) or mini-dose Methotrexate (n=2). Despite a high prevalence of pre-transplant allo-immunization, all fourteen patients achieved sustained donor engraftment. Myeloid recovery (absolute neutrophil count >500cells/uL) occurred at a median 14 days post transplant (range 8-18 days). A conversion from mixed to full donor myeloid and T-cell chimerism Occurred in most patients by 30 days post-transplant. Seven of 13 patients at risk for CMV reactivation developed pp65 antigenemia (KM probability 50%), without any cases of CMV disease. GVHD was the major transplant complication with acute grade 2-4 and 3-4 GVHD occurring in 8/14 (KM probability 56%) and 5/14 (KM probability 35%) patients respectively. Twelve of 14 patients developed chronic GVHD (limited in 11/12), which resolved completely with low-dose alternate day steroids and/or CSA in all but 1 case. One patient who received an allograft from his HLA matched father died 16 months post-transplant from complications related to chronic GVHD. With a median follow up of %17% months (range 5-50 months), 13/14 patients survive in complete remission without chronic GVHD and with full donor chimerism in all lympo-hemtopoietic lineages (KM probability of long-term survival 87.5%. In conclusion, Fludarabine-based nonmyeloablative transplantation can achieve excellent donor engraftment and long-term disease free survival in heavily transfused and allo-immunized patients with ATG refractory SAA and PNH.

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DIALOG(R)File 5:Biosis Previews(R)

0014780352 BIOSIS NO.: 200400147013
HLA-identical sibling peripheral blood stem cell transplantation (PBSCT) for hematological malignancies: Limited GVHD and a 69% 4-years DFS after partial in vitro T-cell depletion with CAMPATH-1H in combination with DLI for CML molecular relapses.
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ABSTRACT: Transplantation with stem cells from an HLA-identical sibling donor is a well-established therapeutic modality for hematological malignancies. Unfortunately, the donor T cells in the graft may cause severe forms of graft-versus-host disease (GVHD). T cell depletion diminishes this risk but is associated with an increased frequency of relapse. We report here the results of a prospective non-randomized study of 37 successive patients transplanted between January 1998 and August 2002, which focused on the question of whether partial T-cell depletion in vitro with CAMPATH-1H in combination with donor lymphocyte infusion (DLI) used for treatment of molecular relapses in chronic myeloid leukemia (CML) would prevent GVHD while preserving the graft-versus-leukemia (GVL) effect. Eighty-nine percent of the patients (median age 40 y (range 18-60 y), M/F ratio=21/16; diagnoses AML=12, ALL=2, CML=11, MDS=3, NHL=5, MM=2, AA=2) received a TBI-based, 8% a BU-based and 3% a CY-based conditioning. GVHD prophylaxis was CSP-MTX+-MP in 30 patients (81%) and CSP-MP+-ATG in 7 patients (19%). All patients received PBSC that had been mobilized with G-CSF 10 mug/kg/d for 6 days and harvested on day 4, 5 and 6. To obtain a partial T cell depletion, patients were infused with the pooled aphereses of days 4 and 5 treated with CAMPATH-1H in vitro, followed by infusion of the unmanipulated apheresis harvested at day 6. The median dose of CD34+ cells infused was 9.6X106/kg (range 3-49X106/kg), the median dose of CD3+ cells was 124X106/kg (range %28%-304X106/kg). Results: All patients engrafted successfully. Neutrophil recovery occurred at a median of 14 days (range 8-21d) and platelet recovery (>50 G/L) at 13.5 days (range 8-27d). Acute GVHD was limited to grade II in 3 (8%) and to grade I in 10 (27%) patients. cGVHD occurred in 9 patients (24%); one patient had extensive disease, one patient suffered from BOOP and 7 had limited disease. Day 100 OS and DFS were 95% (95% CI:88-100%). Eight CML patients and 1 NHL patient were treated with DLI at the first signs of recurring disease, resulting in complete remission in all but 2 CML patients who kept their minimal molecular residual disease with a BCR-ABL/ABL ratio <0.05% as determined by a nested PCR. With a median follow up of 3 years (range 1-5 y), the actuarial 4 year OS is 72% (95% CI:53-94%) and DFS is 69% (95% CI:51-88%). The 100-day and 4-year TRM were 3% and 6% respectively. Conclusion: The results of this pilot study show that partial T-depletion in vitro with CAMPATH-1H in combination with DLI for molecular relapses in CML decreases the incidence of GVHD and TRM, with no negative impact on the DFS.

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DIALOG(R)File 5:Biosis Previews(R)

0014780349 BIOSIS NO.: 200400147010
HLA disparity, graft lymphocyte and CD34+ populations, and CMV serostatus influence umbilical cord blood transplant (UCBT) engraftment rate and event free survival (EFS) in adults.
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ABSTRACT: Other than UCB graft cell dose, factors influencing myeloid engraftment (ANC500) in adults are not well defined. 34 adults, median age 38 years (range: 19-54), with advanced hematologic disorders (%28% patients: IBMTR criteria intermed/high) were consecutively transplanted with single unit HLA-mismatched unexpanded UCB grafts from unrelated donors at this institution during the time period 1998-2003. All patients received full myeloablation and GVHD prophylaxis included CSA/short course Medrol. HLA typing included serologic class I and high-resolution DRB1 analyses until 3/2001 and by low-resolution molecular probes thereafter. All patients received G-CSF 10ug/kg starting at day 0 until attained full myeloid recovery. The median day to ANC500, censored by death, relapse and/or+42 days, was %28% days (range 12-41). The actuarial probability of neutrophil recovery was 88% (95% CI: 76-1001 by day 42. Day to ANC500 and EFS were evaluated (univariate analysis) in relation to HLA class II, degree of HLA mismatch, UCB graft lymphocyte/CD34+ subset populations, and CMV serology. Decreasing HLA disparity (A, B, and DRB1) between UCB graft and recipient was associated with significant improvement in day to ANC500 (p=0.034): HLA-matched 3/6 (median: 36 days), matched 4/6 (%28% days), 5/6 or 6/6 (22 days). Neither HLA-A nor B mis-match at one or both loci had significant effect on day to attain ANC500 (p=0.592 and 0.738). HLA match vs. mismatch at DRB1, however, was associated with a significantly decreased time to ANC500 (median 22 days and 36 days, p=0.019). The median infused UCB nucleated cell dose was 1.9X10e7/kg and CD34+ 1.15X10e5/kg. UCB graft infused cell dose for T cells (CD3+56-) was 5.5X10e6/kg, graft NK cells (CD56+30-) 3.6X10e6/kg, and double positive CD3+56+ UCB graft lymphocytes infused was 2.2X10e6/kg. UCB graft CD45+ infused cell dose was noted to correlate with day to ANC500 (p=0.02). In addition, UCB graft lymphocyte subsets including T cell and double positive CD3+56+ cells correlated with myeloid engraftment (p=0.016 and 0.02). UCB graft T cell subset analysis showed that CD3+4+ cells, not CD3+8+ cells, were associated with faster time to myeloid engraftment (p=0.013). NK cells showed no significant effect on engraftment. Higher graft cell doses of multiple CD34+ subsets including immature (lineage negative) populations and those co-expressing CD38 and HLA-DR were associated with improvement in day to ANC500 (p=0.022). Patients that tested seropositive for CMV had slower myeloid recovery (median 35 days to ANC500) compared with seronegative patients (ANC500 median 22 days)(p=0.015). Effects on EFS were also analyzed using the same parameters. UCB graft HLA class II matching with recipient significantly improved EFS; patients receiving class II matched UCB grafts demonstrating EFS median 271 days, while patients infused with mismatched grafts a median 64 EFS days (p=0.047). Patients testing positive for CMV showed a shorter EFS than those testing negative (65 and 332 days, respectively p=0.05). In summary, UCB graft factors including HLA class II mismatch and increased HLA disparity negatively influence EFS and engraftment in adults undergoing UCBT, while graft T cell and CD3+56+ lymphocytes and CD34+ cells positively influence engraftment rate. This data verifies the importance of HLA matching in UCB graft selection criteria for adults undergoing full myeloablation and UCBT.

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DIALOG(R)File 5:Biosis Previews(R)

0014780343 BIOSIS NO.: 200400147004
Re-addressing autografting in the imatinib era: Filgrastim mediated stem cell mobilization during imatinib therapy in chronic myeloid leukemia patients is feasible and can generate bcr/abl-negative apheresis products.
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ABSTRACT: Despite the remarkable treatment effects of imatinib mesylate in chronic myeloid leukemia (CML) allogeneic stem cell transplantation (SCT) so far remains the only curative approach. Moreover, development of resistance to imatinib, limited availability of matching stem cell donors or an unfavorable risk profile for allogenic SCT reduce the number of therapeutic options in a subset of patients. As a first step to re-evaluate the place of autologous SCT in the imatinib era and to investigate a possible in vivo purging through this substance we performed G-CSF (filgrastim) induced stem cell mobilization (SCM) and subsequent apheresis in 15 chronic phase and 3 accelerated phase CML patients. While in 16 patients (89%) sufficient numbers of CD34+ cells could be mobilized apheresis was successful (gtoreq2.0X106 CD34+ cells/kgBW) in 13 individuals (72%). Interestingely, in the latter cases 5 (%28%%) harvests could be obtained which were negative for bcr/abl mRNA as assessed by nested RT-PCR. Moreover, all except one harvest were negative in 1st round RT-PCR implicating a low level of CML cell contamination. There was no significant change in peripheral bcr/abl transcript load after SCM as assessed by quantitative real-time RT-PCR. 15 patients remained stable in complete cytogenetic remission during a median observation period of 9.3 (range: 3-%17%) months after SCM. One patient achieved molecular remission (MR) shortly after SCM. Another patient who exhibited rising bcr/abl mRNA levels already before SCM achieved CCR after autologous SCT with the generated harvest. One patient with a Philadelphia chromosome-negative, bcr/abl-positive CML showed a hematological relapse 6 months after SCM. We conclude that G-CSF stimulation and subsequent CD34+ cell apheresis under simultaneous imatinib medication is safe and feasible in CML patients. Additionally, we found that by this procedure, stem cell harvests can be generated which exhibit low or non-detectable levels of bcr/abl mRNA.

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DIALOG(R)File 5:Biosis Previews(R)

0014780330 BIOSIS NO.: 200400146991
DLA-haploidentical stem cell allografts after anti-CD44 therapy and nonmyeloablative conditioning: Achievement of full donor chimerism by donor lymphocyte infusion.
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ABSTRACT: Background: We previously reported that engraftment across a dog leukocyte antigen (DLA) haplotype-mismatched barrier can be achieved after reduced-intensity conditioning with 450 cGy total body irradiation (TBI) plus post-grafting mycophenolate mofetil (MMF)/cyclosporine (CSP) when anti-CD44 monoclonal antibody (MAb), S5, is added to the regimen pretransplant (Exp Hematol 2003; 31:168). Here, we studied the effect of anti-CD44 therapy in facilitating engraftment of DLA-haploidentical donor cells after nonmyeloablative conditioning with 200 cGy TBI and prolonged postgrafting immunosuppression. We also studied safety and efficacy of donor lymphocyte infusion (DLI) after nonmyeloablative transplant to increase donor chimerism. Methods: Thirty-three recipient dogs were administered MAb S5, at a dose of 0.2 mg/kg/day from days -7 through -2, before 200 cGy TBI. Unmodified G-CSF-mobilized peripheral blood stem cells (PBSC) from DLA-haploidentical donors were infused followed by immunosuppression with MMF (5-10 mg/kg BID SQ for %28%-101 days) and CSP (15mg/kg BID PO for 102 days). Two dogs received additional weekly methotrexate (0.4 mg/kg IV from days 42 through 105). To increase donor chimerism, 4 dogs received escalating dose of DLI from their donors after transplant. Results: All dogs achieved prompt initial engraftment with donor chimerism of PBMC ranging from 5-98% (median; 59%) 2-3 weeks after transplant. Of %28% dogs who survived for 5 weeks or longer, 13 (46%) had donor engraftment with a median follow-up of >20 (range 5-55) weeks. Fifteen (54%) dogs rejected their donor grafts after discontinuation or dose-reduction of MMF/CSP (5-16 weeks after transplant). Graft rejections occurred later in dogs given prolonged immunosuppression when compared to those treated with shorter courses of immunosuppression (median time to rejection; 13.5 vs. 7 weeks). In 4 dogs, 10 doses of DLI were given 1, 2, or 3 months after transplant. Three of the 4 dogs given DLI achieved conversion to full donor chimerism in T-cell fraction after the third DLI dose (CD3+ cells infused: 1-10X107/kg) administered in the absence of immunosuppression. Subsequent graft-versus-host disease requiring therapy developed in 2 dogs. Conclusions: Initial engraftment of DLA-haploidentical PBSC can be achieved by anti-CD44 therapy and 200 cGy TBI with MMF/CSP. However, half the dogs rejected their donor grafts after discontinuation or dose-reduction of MMF/CSP. DLI from the haploidentical donors facilitated conversion to full donor chimerism after nonmyeloablative HCT, which warrants further studies to evaluate for clinical feasibility.

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DIALOG(R)File 5:Biosis Previews(R)

0014766364 BIOSIS NO.: 200400133718
G-CSF-mobilized hematopoietic stem cells accelerate recovery from acute and chronic carbon tetrachloride (CCl4)-induced liver injury.
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ABSTRACT: The recently recognized potential of bone marrow cells to give rise to hepatocytes has promted us to test whether only G-CSF-primed hematopoietic stem cells could prevent or improve liver damage in an experimental liver injury model. To this goal, C57B16 mice were administered ip G-CSF 200gamma/kgX7 days followed by CCl4 4ml/kg on day 8 and G-CSF for 4 additional days (Group A), G-CSFX7 days and CCl4 on day 8 (Group B) and CCl4 only (Group C). Liver histology, 5 days after CCl4, demonstrated in group A only mild centrolobular necrosis maintaining a rather normal liver architecture (injury grade I-II); in group B moderate necrosis (injury grade I-III), and in group C significant necrosis with severely disrupted architecture (injury grade III-IV). This was accompanied by a survival benefit in the G-CSF-treated groups, A and B, compared to control group C (mortality rate 6.25% vs %28%.6%, respectively). Fifteen days after CCl4, liver histology was normal in group A and B, while in group C necrosis could still be detected. We also tested the G-CSF effect in a liver fibrosis model generated by biweekly ip injections of CCl4 2ml/kg for 2 months. Group I and group III received CCl4 for 2 months and group II received CCl4 for 2 months plus G-CSF for 8 days. Group I and II were sacrificed 9 days after last CCl4 dose and group III was sacrificed one month after last CCl4 dose. Liver histology, demonstrated typical cirrhosis in group I, while group II livers appeared relatively normal with fewer nodules and less well defined fibrous septae. Group III livers, had normal architecture with only occasional short fibril fragments. Since spontaneous recovery occurs in the CCl4-treated group although with a little delay, in both the acute and the chronic liver injury model, we further explored to which degree this regeneration is liver-endogenous or bone marrow-derived and whether the acceleration in recovery observed in G-CSF-treated mice is due to the mobilized hematopoietic stem cells. Female, lethally irradiated C57B16 recipients, were transplanted with whole bone marrow from male donors. 40 days post BMT, one group of mice received 7 doses of G-CSF before CCl4 and 4 doses after CCl4 and another group was used as control and received CCl4 only. An indirect immunohistochemical method for sry protein detection based on streptavidin-peroxidase complex, demonstrated clusters of periportally and pericentrally arranged, donor-derived hepatocytes in both groups. 0.7% of the total hepatocytes were positive for the sry protein in the control group whereas 1.7% of the total hepatocytes were of donor origin in the G-CSF-treated group. Overall, these data suggest that liver recovery after necrosis is basically liver-endogenous and in a lesser degree bm-derived. G-CSF ameliorates CCl4-induced acute and chronic liver injury and accelerate the regeneration process by mobilizing hematopoietic stem cells that home to injured liver, although pharmacological effects of G-CSF other than mobilization, cannot be excluded. Experiments to further explore the underlying mechanisms of G-CSF effect in damaged liver are underway. However, regardless of what is the underlying process of this restoration, the potential of treating acute and chronic liver diseases in humans is important.

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DIALOG(R)File 5:Biosis Previews(R)

0014766116 BIOSIS NO.: 200400133470
Pregnancies in patients with severe chronic neutropenia.
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ABSTRACT: Pregnancies in women with neutropenia are associated with several risks: (1) the neutropenic mothers' continuing risk of contracting bacterial infections during pregnancy, (2) the risk of passing bacterial infections on to the fetus potentially causing miscarriages, (3) the risk of transferring infections to the newborn during delivery causing newborn infections, and (4) the risk of children inheriting congenital or cyclic neutropenia from their mothers. Since 1994, the Severe Chronic Neutropenia International Registry (SCNIR) has collected data on more than 140 pregnancies in neutropenic mothers (7 congenital, 50 cyclic, 82 idiopathic). G-CSF treatment varied within the neutropenic categories and with the availability of G-CSF: 5 of the 7 (71%) congenital mothers, %17% of the 33 (34%) cyclic mothers, and 9 of the 82 (11%) idiopathic mothers received G-CSF during pregnancy. The pattern of G-CSF administration varied with respect to the duration (median duration was 2 trimesters), the dose given (median 2.7 mcg/kg/d; range 0.2 to 12 mcg/kg/d), and the frequency of administration (daily, alternate day, weekly, every other week, as needed). The percentage of live births was the same (70%) in both the G-CSF treated and non-treated group. The number of spontaneous abortions was slightly higher in the untreated group, i.e., 22%, compared to 13% spontaneous abortions among G-CSF treated women. Neonate complications occurred in approximately 4% of all live births-all of them in children from untreated mothers. Congenital abnormalities were reported neither in the G-CSF treated nor in the non-treated patients. In conclusion, administration of G-CSF during the last weeks of the third trimester appears to prevent maternal infections that could be passed on to the newborn during labor and cause neonate complications. This data from the SCNIR indicates that it is safe to treat neutropenic pregnant women with G-CSF.

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DIALOG(R)File 5:Biosis Previews(R)

0014766035 BIOSIS NO.: 200400133389
Prophylactic G-CSF and GM-CSF decrease febrile neutropenia following chemotherapy in children with cancer: A meta-analysis of randomized controlled trials.
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JOURNAL: Blood 102 (11): p251a November 16, 2003 2003
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ABSTRACT: Background: The role of hematopoietic colony stimulating factors (CSFs) in children with cancer is unclear. Our primary objective was to determine whether prophylactic CSF reduces the rate of febrile neutropenia in children with cancer. Our secondary objectives were to determine whether prophylactic CSF reduces the duration of hospitalization, rate of documented infections, duration of parenteral antibiotics, amphotericin B use, or infection-related morality. Data Sources: Medline (1966 to July 2003) and EMBASE (1980 to July 2003) searches were supplemented with a hand search of references and major conferences, and contact with the pharmaceutical manufacturers of CSFs. Study Selection: Studies were included if the study population consisted of children, or if data was extractable for those ltoreq18 years of age, if there was a randomization between CSF and placebo/no therapy, if CSF was administered in the prophylactic setting (before the onset of neutropenia or febrile neutropenia), and if the chemotherapy preceding CSF was identical to that preceding placebo/no therapy. From the 971 reviewed articles, 16 studies were included. Data Extraction: Two investigators independently extracted data on study characteristics, validity and primary and secondary outcomes. Data Synthesis: The mean rate of febrile neutropenia in the control arms was 57% (range 39 to 100%). Using a random effects model, CSF use was associated with a reduction in febrile neutropenia, with a rate ratio of 0.80 (95% CI 0.67, 0.95; p=0.01), and a decrease in the length of hospitalization, with a weighted mean difference of -1.9 (95% CI-2.7, -1.1) days; p<0.00001. CSF use was also associated with a reduction in documented infections (rate ratio 0.78 (95% CI 0.62, 0.97; p=0.02)) and a reduction in amphotericin B use (rate ratio 0.50 (95% CI 0.%28%, 0.87; p=0.02)). There was no difference in duration of parenteral antibiotic therapy (weighted mean difference -4.29 (95% CI-10.60, 2.02) days; p=0.2) or infection-related mortality (rate ratio 1.02 (95% CI 0.34, 3.06; p=0.97)). Conclusions: We have demonstrated that prophylactic CSFs in children with cancer reduced the rate of febrile neutropenia by 20% and decreased the duration of hospitalization by approximately 2 days. CSFs also reduced the rate of documented infection by 22% and amphotericin B use by 50%. However, CSFs were not associated with a reduction in infection-related mortality. Prophylactic CSF should be considered when the expected rate of febrile neutropenia gtoreq40%.

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DIALOG(R)File 5:Biosis Previews(R)

0014766023 BIOSIS NO.: 200400133377
A new preparative regimen for older patients with aggressive CD20-positive B-cell lymphoma utilizing standard-dose Yttrium-90 Ibritumomab Tiuxetan (Zevalin(R)) radioimmunotherapy (RIT) combined with high-dose BEAM followed by autologous hematopoietic cell transplantation (AHCT): Targeted intensification without increased transplant-related toxicity.
AUTHOR: Fung Henry C (Reprint); Forman Stephen J (Reprint); Nademanee A (Reprint); Molina A (Reprint); Yamauchi D (Reprint); Speilberger R; Kogut N; Sahebi F; Parker P (Reprint); Rodriguez R (Reprint); Krishnan A (Reprint); Popplewell L (Reprint); Wong J (Reprint); Raubitschek A (Reprint)
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ABSTRACT: Background: AHCT is an effective treatment for patients (pts) with poor-risk aggressive B-cell lymphoma (Ag-NHL). Approximately 30-40% pts with relapsed Ag-NHL can achieve durable remissions after AHCT, with disease progression accounting for most of the treatment failures. Attempts at further dose intensification of transplant regimens have been limited by unacceptable toxicity, in particular for older pts who also tend to have an unfavorable prognosis. Although Zevalin was only FDA-approved for the treatment of low grade CD20+ve B cell lymphoma, the initial phase I study showed that pts with Ag-NHL had a 58% response rate to this therapy. In an attempt to improve treatment outcome in older pts undergoing AHCT for poor risk aggressive CD20+ve B-cell lymphoma, we designed a preparative regimen using the combination of standard dose Zevalin (0.4mg/kg) and high-dose BEAM (carmustine, etoposide, cytarabine

and melphalan) for older pts with Ag-NHL. Methods: Between 5/02 and 4/03, 12 pts were enrolled in this pilot study. Patients with poor risk Ag-NHL who are gtoreq55 year old (n=10) or had received prior dose limiting radiation that preclude total body irradiation (n=2) were eligible for this study. All eligible pts undergo routine imaging studies on day -21 with 111Indium-Zevalin and therapy on day -14 at a fixed dose of 0.4 mci/kg of 90Yttrium-Zevalin. Dosimetry was not performed. BCNU 300mg/m2 was then given on day -6; cytarabine 800mg/m2 and etoposide 800mg/m2 were given between day -5 to day -2 followed by and Melphalan 140mg/m2 on day -1. On day 0, a minimum of 3.0X106 CD34+ cells/kg was re-infused. G-CSF 5m g/kg was prescribed daily beginning on day +5. The median age at AHCT was 61 years (range, 20-78). Histology: mantle cell lymphoma-5; diffuse large cell lymphoma-7 (2 had co-existing follicular large cell lymphoma). Disease status prior to AHCT: induction failure-5; 1st relapse/2nd CR-3; 3rd CR/2nd relapse-2. Two pts with MCL underwent AHCT in 1st remission. Ten pts had both PET and indium scans prior to AHCT for evaluation. Five had a +ve PET scan and 3 of them were also positive by indium scans. Results: All pts tolerated the regimens well with only two Grade III/IV G.I. toxicities. One pt developed steroid-responsive interstitial pneumonitis %17% days after AHCT. All pts engrafted promptly after AHCT. The median day for reaching an ANC of >1000 and platelet >20,000 was 11 days (range 10-13) and 11 days (range 10-15), respectively. The median total dose of 90Y Zevalin was 32 mCi (range: 20.7-40). With a median follow-up of 9 months (range: 4-15), only 1 pt with MCL has died of progressive disease. All remaining 11 pts are well without evidence of lymphoma by CAT scan and PET scan at last follow-up. Conclusions: We conclude that 1) the combination of standard-dose 90Yttrium-Zevalin and high-dose BEAM followed by AHCT can be given safely without dosimetric guidance for older pts with aggressive CD20+ve lymphoma; 2) this approach is well tolerated and allows for targeted intensification of the conditioning regimen without increased transplant-related toxicity; 3) although longer follow-up is warranted, these results look promising, considering the age and the refractory status of this pt cohort.

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DIALOG(R)File 5:Biosis Previews(R)

0014766021 BIOSIS NO.: 200400133375
Long term survival after autologous stem cell transplant (ASCT) in AIDS related lymphoma patients.
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ABSTRACT: Introduction: High Activity Antiretroviral Therapy (HAART) has improved the outcome of AIDS patients (Pt) and also allowed to increase treatment intensity in AIDS-related lymphoma (ARL), improving therapeutic response and survival rates. Patients and Methods: 14 male ARL Pt (3 HD/11 NHL) entered ASCT programme. Median age was 39.5 years, ECOG<3 and all responded to HAART. Eligible ARL criteria for recruitment included: >1st complete remission (CR) (3 Pt), 1st CR that needed more than 1 line of therapy (3 Pt), 1st CR with IPI>=2 (2 Pt), Burkitt type undertreated in 1st CR (2 Pt) and chemosensitive partial remission (PR) (4 Pt). Mobilization schedules used were: G-CSF 20mcg/kg/d (7 Pt), G-CSF 10mcg/kg/d (1 Pt), CTX 1.5 grs/m2X1 day plus G-CSF 20mcg/kg/d (3 Pt) and ARA-C plus G-CSF (3 Pt). Hematopoietic Stem Cells (HSC) were collected and stored in an isolated chamber at -80degreeC, after programmed criopreservation, for a median of 36 days (16-69). Three mobilized Pt died before ASCT (1Pt VHC disease and 2 Pt ARL progression). ASCT was performed in 11 Pt (8 NHL and 3 HD). Conditioning regimen used were BEAM (10)/BEAC (1). HAART was maintained during mobilization and ASCT. G-CSF after ASCT was started at a median of day +12 (7-21) and maintained a median of 6 days (2-32). Results: Median of CD34+ cells collected was 4.7X106/kg (1.8-21.2). Median time to reach PMN >0.5X109/L was 16 days (9-33) and 20 days (11-36) for platelets >20X109/L. 1 Pt died before reaching platelet >20X109/L (UPN TiPJGG) and Pt GM160 became transfusion independent since day +49 but with platelet counts <20X109/L for 1 year. Immune status, HIV viral load (VL) evolution and ARL follow up are given. Toxicity and infectious events: 11/11 Pt had neutropenic fever (1 bacterial pneumonia, 1 lung aspergillosis, 4 bacteriemias and 5 fever of unknown origin). 1 Pt had herpes zoster 1 year after ASCT. Grade II mucositis occurred in 5 of 8, grade II hepatic toxicity occurred in 1 of 8 Pt. Pt TiPJGG died 20 days after transplant due to ARL progression. Pt MV595397 is alive in relapse and Pt GM136 relapsed 34 months after ASCT. The remaining 8 Pt are alive and in CR with a median follow-up of 21 months (1-%28%). Conclusions: HSC collected in ARL Pt showed an adequate number of CD34+ cells to perform ASCT. Mobilization and conditioning programmes did not increase HIV VL, as long as HAART was maintained. ASCT was not associated with an increased intensification related toxicity and opportunistic infections. In this study ASCT is associated with long term disease free survival in 73% of ARL Pt.

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DIALOG(R)File 5:Biosis Previews(R)

0014765997 BIOSIS NO.: 200400133351
A phase I/II study of mycophenolate mofetil (MMF) in combination with cyclosporine (CSP) for prophylaxis of graft versus host disease (GVHD) after myeloablative conditioning and allogeneic hematopoietic cell transplantation (HCT): Dose escalation of MMF.
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ABSTRACT: MMF in combination with CSP was effective for preventing GVHD in preclinical studies and may be associated with less toxicity than methotrexate (MTX) (Blood 91:2581, 1998). From 1999-2002, 46 patients ltoreq65 years old with advanced hematological malignancies or myelodysplastic syndrome received CSP/MMF for GVHD prophylaxis after a myeloablative conditioning regimen and HCT from HLA-matched related donors. The source of stem cells was G-CSF-mobilized peripheral blood in 45 patients and marrow in 1 patient. CSP was administered at 3 mg/kg/day i.v. and at 12.5 mg/kg/day p.o. and adjusted based on blood levels. In the phase I portion of the study, MMF was administered from day 0-27 at 15 mg/kg every 12 hours (group A; n=10), every 8 hours (group B; n=11) and every 6 hours (group C; n=10). The intravenous formulation of MMF was administered to all patients for at least 14 days. The steady state clearance (Css) of mycophenolic acid (MPA) was significantly increased with increasing daily doses of MMF. Time to engraftment after HSCT was not appreciably affected by the increased daily dose of MMF and was less

than what has been reported in studies with CSP/MTX (median=16 days). Mucositis was mild, and there was no increase in stool volumes at each dose level. One patient in group C had significant gastrointestinal toxicity. Although the numbers were limited at each dose level, a dosing interval of 8 hours (group B) was associated with the lowest incidence of acute GVHD. Since similar levels of MPA were achieved to that required for solid organ transplantation and a lower level of acute GVHD was observed, a further 15 patients were added to group B at this dose of MMF (group D). In group D, the time to engraftment was 15 (10-20) days. The incidence of grade II-IV acute GVHD was 62% (16/26) with a median onset of 15 (8-48) days after HSCT. Grade III-IV GVHD occurred in 4 patients (15%). Three patients required secondary therapy for acute GVHD. In a cohort of patients receiving CSP/MTX for GVHD prophylaxis (n=36) who had advanced hematological malignancies and were matched for time of transplant and source of stem cells from a HLA-identical sibling donor, the incidence of grade II-IV and grade III-IV GVHD was 70% and %17%%, respectively. The day 100 mortality was 40%, 36%, 40% and 23% for group A, B, C and D, respectively. In conclusion, an adequate Css of MPA was achieved in group B with the intravenous formulation of MMF and a dosing interval of every 8 hours. The incidence of acute GVHD in patients receiving GVHD prophylaxis with CSP/MMF was comparable to that observed with CSP/MTX. MMF may be a useful agent to be used in combination with CSP for GVHD prophylaxis since toxicities may be less than with MTX and it can be administered safely to patients with hepatic and renal dysfunction.

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DIALOG(R)File 5:Biosis Previews(R)

0014765995 BIOSIS NO.: 200400133349
Outcomes of graft failure/rejection following allogeneic hematopoietic cell transplantation: 10-Year experience at FHCRC.
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ABSTRACT: Background: Although outcomes were poor among historic patients who experienced graft failure/rejection (GF) after allogeneic hematopoietic cell transplantation (HCT), we reasoned that outcomes may have changed among more recent patients with advances in supportive care and HCT with nonmyeloablative conditioning. Patients and Methods: We reviewed medical records of 2501 patients with malignancies given their first allogeneic HCT at FHCRC between 1993 and 2002 who survived for %28% days or more after HCT. Conditioning included either conventional myeloablative (n=2269) or nonmyeloablative regimens with 2 Gy TBI+fludarabine (n=232). Patients received marrow (n=1674), G-CSF mobilized PBSC (n=804), or cord blood (n=23) from either HLA-matched (n=1147) or mismatched (n=241) relatives or unrelated volunteers (n=1113), and 64 received T-cell depleted or CD34-positively selected grafts. Primary GF was defined as failure of the ANC to surpass 500/mm3 or the absence of donor T-cells (ltoreq5%) as determined by testing for chimerism with the use of VNTR polymorphism or FISH before relapse, disease progression, second HCT, or death. Secondary GF was defined as a decrease in the ANC to less than 100/mm3 on at least 3 consecutive determinations at least one day apart or the absence of donor T-cells (ltoreq5%) after initial engraftment without recovering before relapse, disease progression, second HCT, or death. Results: Ninety-one patients (3.6%) experienced primary GF (n=57; median %28% (range 20-36) days) or secondary GF (n=34; median 60 (range 33-496) days). Overall survival after GF following nonmyeloablative HCT (n=21; 52%) was significantly higher than that following conventional HCT (n=70; 20%). Among 91 patients with GF, 20 died before any therapy could be attempted, 29 experienced reconstitution of autologous hematopoiesis, 48 underwent second HCT from the original (n=33) or alternate donors (n=15) a median of 60 (range 29-1625) days after the first HCT, and 4 patients received autologous stem cells. Nonmyeloablative HCT recipients were more likely to experience autologous reconstitution (86% vs 16%), while conventional HCT recipients were more likely to die within 30 days after GF (31% vs 5%) or receive second HCT (60% vs 29%). Conditioning for second HCT consisted either of myeloablative regimens (n=6) or immunosuppressive drugs including anti-CD3 antibody BC3 plus high-dose glucocorticoids (n=31) or other combinations (n=11). After second HCT, 33 (69%) patients engrafted, 7 (15%) died without engraftment, and 7 (15%) experienced autologous reconstitution. Overall, 25 of 91 patients (27%) are surviving (16 after second HCT) with a median follow-up of 1580 (range 186-3441) days after first HCT; 14 disease-free. Sixty-six patients (73%) died a median of 88 (range %28%-2245) days after first HCT; causes of death included fungal infections (n=22), other infections (n=8), relapse (n=12), GVHD (n=12; 10 after second HCT), and other causes (n=12). Multivariate analysis showed conventional conditioning for first HCT, greater patient age, sex mismatch, diagnosis of acute leukemia, disease risk, CMV serostatus, and acute GVHD after first HCT were associated with increased risks for mortality after GF. Conclusions: Outcomes of GF after nonmyeloablative HCT were better than those after conventional HCT primarily due to a greater likelihood of autologous reconstitution in the nonmyeloablative group resulting in less early death after GF.

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DIALOG(R)File 5:Biosis Previews(R)

0014764767 BIOSIS NO.: 200400132121
Interferon treatment outcomes in patients with decompensated HCV+cirrhosis.
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ABSTRACT: HCV+cirrhosis has a 50% mortality in 5 years once decompensation occurs. Hepatits C in one of the most common indications for liver transplantation. Survival after liver transplantation is reduced in patients with HCV, compared to other patients. Current treatment of chronic hepatitis C results in viral clearance in 40% to 80% of treated individuals. However, only well compensated cirrhotics have been included in the large randomized trials. There is limited data concerning the treatment of hepatitis C in decompensated cirrhosis. The aims of this study were to evaluate the efficacy of interferon (IFN) based treatment, the incidence and severity of adverse effects in HCV+cirrhotics, particularly those with decompensation, as well as the effect of pretransplant treatment on HCV recurrence after transplantation. Methods: 77 HCV+cirrhotic patients treated over the last 5 years by the hepatology service at Loyola University Medical Center were identified that had either completed treatment and had a 6 month follow up after end of treatment or had stopped treatment because of side effects. These patients received one or another IFN based treatment with or without ribavirin (RIBA). Using standard drug trial criteria for the definition

of compensated cirrhosis, this group of treated patients was divided into 2 groups: 1) 48 compensated patients and 2) 29 decompensated patients. Another 20 liver transplant (OLT) candidates with HCV+cirrhosis that did not receive treatment or refused treatment were studied as an untreated control group. Results: There were significant differences between the three groups of patients in albumin, total bilirubin, prothrombin time and Child-Pugh score. The median length of treatment was %17%.2 months in the compensated patients and 12.7 months in the decompensated patients (p=0.01). The end of treatment response (ETR) was 65% and 48% for compensated and decompensated patients, respectively (n.s.). The sustained viral response (SVR) was 40% and 31% for compensated and decompensated patients, respectively (n.s.). There were 26 treated patients that were also OLT candidates. 11 had a SVR and 15 did not. 6 patients with a SVR were transplanted and none had recurence of HCV after transplantation. 6 patients that did not clear HCV were transplanted and all had recurrence of HCV after transplantation. A total of 6 patients (8%) stopped treatment due to adverse effects, 2 in the compensated group (4%) and 4 in the decompensated group (14%). 20 patients (42%) in the compensated group had Hb <10 and 11 in the decompensated group (38%). Almost all patients received erythropoietin. 4 and 2, in each group respectively, stopped RIBA. 8 compensated patients (%17%%) and 12 decompensated patients (41%) had WBC <2.0. Almost all received G-CSF. Infections occurred in 11 compensated patients (21%) and in 10 decompensated patients (34%). Hospital admission was necessary in approximately half of the infections, but no deaths occurred due to infection. 9 patients in the untreated group (45%) had infections, with one death. No patient had platelet count < 20,000. A total of 20 patients developed depression (26%). 2 patients with a previous history requiered psychiatric admission, the rest were treated as outpatients. Other adverse effects included hyper- or hypothyroidism in 14 patients (18%), dehydration requiering IV fluids in 7 patients (18%), new onset of diabetes mellitus or increased need for antidiabetic medication in 4 (5%) and hepatic encephalopathy in 7 patients (18%). Conclusions: 1) Decompensated HCV+cirrhotic patients can be treated successfuly with IFN based therapy with SVR rates comparable to those achieved in well compensated cirrhotics. 2) Growth factors are needed in approximately half of patients to prevent anemia and severe leucopenia. 3) Adverse effects are frequent and can be severe. 4) HCR-RNA negativity in patients with SVR prior to OLT persists after transplantation.

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DIALOG(R)File 5:Biosis Previews(R)

0014588366 BIOSIS NO.: 200300544556
Immune reconstitution following reduced-intensity transplantation with cladribine, busulfan, and antithymocyte globulin: Serial comparison with conventional myeloablative transplantation.
AUTHOR: Saito T; Kanda Y; Nakai K; Kim S-W; Arima F; Kami M; Tanosaki R; Tobinai K; Wakasugi H; Heike Y; Mineishi S; Takaue Y (Reprint)
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JOURNAL: Bone Marrow Transplantation 32 (6): p601-608 September 2, 2003 2003
MEDIUM: print
ISSN: 0268-3369 _(ISSN print)
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The primary object of the conditioning regimen for allogeneic reduced-intensity stem cell transplantation (RIST) is immunosuppression to achieve stable engraftment of donor cells, rather than bone marrow ablation. Therefore, immune reconstitution after RIST might be different from that after conventional stem cell transplantation (CST). In this study, 22 patients underwent RIST and %28% underwent CST. The RIST regimen consisted of cladribine (2-CdA; 0.11 mg/kg/day for 6 days), BU (4 mg/kg/day for 2 days), and rabbit anti-thymocyte globulin (ATG; 2.5 mg/kg/day for 2-4 days). The CST group received either the BU (4 mg/kg/dayX4 days)/CY (60 mg/kg/dayX2 days) (n=13) or CY (60 mg/kg/dayX2 days)/TBI (4 Gy/dayX3 days) regimen (n=15). All patients underwent transplantation with G-CSF-mobilized blood stem cells. Engraftment speed after RIST was fast and seven of 22 patients did not require platelet transfusion. We noted that the numbers of CD4+, CD4+ CD45RA+, and CD4+ CD45RO+ T cells after transplant in the RIST group were significantly lower than those in the CST group (P=0.0001 for both the comparisons). However, the reconstitution of CD20+ B cells was faster in the RIST group (P=0.0001). The response of T cells to PHA stimulation was lower in the RIST group (P=0.0001 on day 30 and P=0.02 on day 90). Nevertheless, there were no significant differences in the incidence of bacterial, fungal, or viral infections between the two groups. We concluded that our RIST regimen might delay laboratory-evaluated T-cell immune reconstitution compared to CST; however, the observed setbacks did not directly translate into clinically significant increases in infectious episodes.

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DIALOG(R)File 5:Biosis Previews(R)

0014585104 BIOSIS NO.: 200300541294
An animal model of atopic dermatitis: cDNA microarray analyses of mRNA in chronic lesional skin delineate a balanced Th1/Th2 inflammatory cytokine profile.
AUTHOR: Chen L (Reprint); Chan L (Reprint)
AUTHOR ADDRESS: Dermatol and Micro/Immunol, UIC, Chicago, IL, USA**USA
JOURNAL: Journal of Investigative Dermatology 121 (1): p0088 July 2003 2003
MEDIUM: print
CONFERENCE/MEETING: International Investigative Dermatology 2003 : Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology and Society for Investigative Dermatology Miami Beach, Florida, USA April 30-May 04, 2003; 20030430
SPONSOR: European Society for Dermatological Research
ISSN: 0022-202X _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

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DIALOG(R)File 5:Biosis Previews(R)

0014501813 BIOSIS NO.: 200300470532
A multicenter, open, non-comparative, phase II study of the combination of cladribine (2-chlorodeoxyadenosine), cytarabine, and G-CSF as induction therapy in refractory acute myeloid leukemia: A report of the Polish Adult Leukemia Group (PALG).
AUTHOR: Wrzesien-Kus A; Robak T (Reprint); Lech-Maranda E; Wierzbowska A; Dmoszynska A; Kowal M; Holowiecki J; Kyrcz-Krzemien S; Grosicki S; Maj S; Hellmann A; Skotnicki A; Jedrzejczak W; Kuliczkowski K
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JOURNAL: European Journal of Haematology 71 (3): p155-162 September 2003 2003
MEDIUM: print
ISSN: 0902-4441 _(ISSN print)
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objectives: To evaluate the efficacy and toxicity of cladribine (2-chlorodeoxyadenosine, 2-CdA), cytarabine (Ara-C), and granulocyte-colony stimulating factor (G-CSF) (CLAG) regimen in refractory acute myeloid leukemia (AML) in the multicenter phase II

study. Methods: The induction chemotherapy consisted of 2-CdA 5 mg/m2, Ara-C 2 g/m2, and G-CSF. In the case of partial remission (PR), a second CLAG was administered. Patients in complete remission (CR) received two consolidation courses based on HD Ara-C, mitoxantrone or idarubicine, with or without 2-CdA. Results: Fifty-eight patients from 11 centers were registered; 50 primary resistant and eight early relapsed (CR1 <6 months). CR was achieved in 29 (50%) patients, 19 (33%) were refractory, and 10 (%17%%) died early. Forty of 50 primary resistant patients received daunorubicin (DNR) and Ara-C as the first-line induction therapy (DA-7), 10 received additional 2-CdA (DAC-7). The CR rates after CLAG were 58% and 10%, respectively in each group (P=0.015). Five of six patients with myelodysplastic syndrome (MDS)/AML achieved CR. Hematologic toxicity was the most prominent toxicity of this regimen. The overall survival (OS, 1 yr) for the 58 patients as a whole, and the 29 patients in CR were 42% and 65%, respectively. Disease-free survival (DFS, 1 yr) was 29%. Only first-line induction treatment with DA-7 significantly influenced the probability of CR after CLAG. None of the analyzed factors significantly influenced DFS and OS. Conclusion: CLAG regimen has significant anti-leukemic activity and an acceptable toxicity in refractory AML. The addition of 2-CdA to the first-line induction treatment may worsen the results of salvage with CLAG. The high CR rate in patients with MDS preceding AML deserves further observation.

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DIALOG(R)File 5:Biosis Previews(R)

0014470765 BIOSIS NO.: 200300425609
The effect of leptin on engraftment in patients undergoing peripheral blood stem cell transplantation.
AUTHOR: Ataergin Selmin; Arpaci Fikret (Reprint); Turan Mustafa; Ozet Ahmet ; Yilmaz M Ilker; Ozata Metin; Ozturk Bekir; Komurcu Seref; Ulutin Cuneyt
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JOURNAL: Haematologia 32 (4): p389-396 2002 2002
MEDIUM: print
ISSN: 0017-6559
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Aim and background: To evaluate the alterations of serum leptin levels during stem cell transplantation and its possible role in engraftment. Thirty-two patients (19 male, 13 female) with various hematological and solid tumors and %28% healthy subjects (15 male, 13 female) as a control group were enrolled in the study. Methods: Serum leptin levels were measured on the day before administering G-CSF, at the time of leukapheresis harvest, on day +1st and +7th after transplantation and on the day of leukocyte engraftment. Results: There was no significant difference in serum leptin levels between patients (mean+-SEM, 11.62+-2.75 ng/ml) before transplantation and control groups (9.79+-1.73 ng/ml). Pre-G-CSF (baseline) level of serum leptin (11.62+-2.75 ng/ml) was significantly decreased to 7.73+-2.02 ng/ml at the time of apheresis harvest (P=0.0029). Later, serum leptin levels increased to 16.75+-3.26 ng/ml on day +1 after transplantation (P<0.0001). Subsequently serum leptin levels both on day +7th posttransplant (12.11+-2.%17% ng/ml) and leukocyte engraftment day (9.26+-1.50 ng/ml) were gradually decreased. There was no correlation between the serum leptin levels and the leukocyte or platelet engraftment. Conclusion: The present study concludes that serum leptin level does not change remarkably during peripheral blood stem cell transplantation and no association exists between circulating leptin levels and the onset of engraftment suggesting that circulating serum leptin does not have a significant direct influence on engraftment.

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DIALOG(R)File 5:Biosis Previews(R)

0014410294 BIOSIS NO.: 200300369013
Use of Herpes Simplex Virus Type 1 Vectors for MnSOD Gene Transfer to CD34+Thy-1+lin- Human Cord Blood Cells.
AUTHOR: Goff Julie P (Reprint); Shields D S (Reprint); Wechuck J B (Reprint); Huang S (Reprint); Wolfe D (Reprint); Epperly M E (Reprint); Glorioso J C (Reprint); Greenberger J S (Reprint)
AUTHOR ADDRESS: Radiation Oncology, University of Pittsburgh, Pittsburgh, PA, USA**USA
JOURNAL: Blood 100 (11): pAbstract No. 5529 November 16, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expansion of hematopoietic stem cells (HSC) in vitro remains a challenge. A critical function of HSC is their capacity to sustain prolonged periods in quiescence within the hematopoietic microenvironment. Maintenance and stability of quiescence of stem cells is critical for successful bone marrow transplantation, prevention of stem cell exhaustion, and genotoxic stress. The self-renewal capacity and plasticity of stem cells have made HSC promising targets for gene therapy and the ability to deliver therapeutic genes to HSC provides potential for the treatment of many acquired and genetic diseases. Previous studies have shown that Herpes Simplex Virus 1 (HSV) is an ideal vector for gene delivery to HSC, particularly in its ability to transduce HSC with no prior stimulation. Manganese Superoxide Dismutase (MnSOD) is a potent cytoprotective antioxidant protein. Increased expression of MnSOD in cells in vitro or in vivo protects cells from irradiation damage, TNF-alpha, interleukin 1 and some chemotherapeutic drugs. We investigated the ability of a replication-defective HSV vector that expresses MnSOD and the GFP reporter gene to transduce human cord blood CD34+ and CD34+Thy-1+lin- (lin-) cells, and the effect on quiescence and proliferation/ differentiation capacity of the two cell populations. CD34+ and lin- cells were transduced with the MnSOD expressing vector, GFP control vector or mock transduced in serum-free medium containing SCF and TPO for 18 hours. Transduced cells were plated in methylcellulose containing SCF, GM-CSF, Il-3, IL-6, G-CSF, and EPO. Colonies (BFU-E, CFU-GM, and CFU-GEMM) were scored on days 7 and 14. Lin- cells transduced with the MnSOD vector were selected by micromanipulation based on GFP intensity and plated at one cell / well in Terasaki plates in serum-free medium with FLT-3L and TPO. Each well containing a single cell was monitored daily for seven days for evidence of cell division. When a division was detected, daughter cells were separated by micromanipulation and placed in different wells on irradiated pre-formed AFT024 stroma with IL-7 (20ng/ml), SCF (10ng/ml), FLT-3L (10ng/ml) to asses proliferative capacity of transfected daughter cells. During the 7 days that single lin- cells were monitored 56% of the non-transduced lin- cells divided. Between 9% and 19% of the MnSOD vector transduced cells divided. The daughter cells were separated and transferred to stroma. None of the transduced lin- cells proliferated on stroma after %28% days compared to greater that 75% of control cells. After 14 days, non-transduced CD34+ cells gave rise to approximately four more colonies than vector transduced cells. There was no statistical difference in colony numbers between cells transduced with the GFP control vector and the MnSOD vector. BFU-E, CFU-GM, and CFU-GEMM colonies were observed in all groups. These data show that CD34+ cells and CD34+Thy-1+lin- can be transduced with HSV vectors expressing MnSOD and that the clonogenic capability of CD34+ cells remains. The question of whether replication-defective HSV vectors expressing MnSOD alters the biologic activity, particularly the question of altered quiescence of more primitive lin- cells remains.

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DIALOG(R)File 5:Biosis Previews(R)

0014410256 BIOSIS NO.: 200300368975
Determinants of High and Low CD 34 Yield after CAD as Part of Total Therapy II (TT II) for Newly Diagnosed Multiple Myeloma (MM): Effect of Thalidomide (THAL).
AUTHOR: Cottler-Fox Michele (Reprint); Barlogie Bart (Reprint); Anaissie Elias (Reprint); Zangari Maurizio (Reprint); Fassas Athanasios (Reprint); Lee Choon-Kee (Reprint); Rhee Frits van (Reprint); Thertulien Raymond (Reprint); Tricot Guido (Reprint)
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JOURNAL: Blood 100 (11): pAbstract No. 5491 November 16, 2002 2002
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CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: TT II evaluates, in a randomized trial design, the contribution of THAL to improving CR, event-free survival (EFS) and overall survival (OS). Induction therapy included CAD with PBSC collection (4 day continuous infusions of CTX 750 mg/m2/d and ADR 15 mg/m2/d plus DEX 40 mg x 4 plus G-CSF) following VAD and DCEP. A collection target of 20 x 106 CD 34/kg was attempted so that 10 x 106 CD 34/kg would be available for future salvage therapy. Typically, 2 - 3 x 106 CD 34 cells/kg were used with Tx-1 and a higher dose of 5 - 8 x 106 CD 34 cells/kg with Tx-2 to ensure rapid hematologic recovery and timely application of consolidation therapy. The minimum CD 34 quantity necessary for 2 Tx was 5 x 106 CD 34/kg available in 83% of the patients; 54% collected at least 20 x 106 and %17%% in excess of 30 x 106/kg. Factors associated with both HIGH YIELD (> 30 x 106/kg) and with LOW YIELD (< 5 x 106/kg) were examined on univariate and multivariate (MV) analysis. HIGH YIELD was associated with B2M < 4 mg/L, LDH 150,000/muL and absence of THAL (B2M THAL significant on MV). LOW YIELD was associated with age > 65 yr, B2M > 4 mg/L, cytogenetic abnormalities of chromosomes 6 (CA 6) and 20 (CA 20) and failure to respond to VAD and DCEP. Older age, CA 20, drug resistance and high B2M were independently adverse features on MV. Thus, THAL dampens high CD 34 yields but does not contribute to failure to collect (< 5 x 106/kg CD 34 cells). The adverse consequences of MM features (drug resistance, B2M and CA 20) for hematopoietic stem cell mobilization attest to the recently recognized interation between MM and hematopoiesis. The higher failure rate of adequate CD 34 collection in 38% of older versus 15% of younger patients (p=.004) may reflect aging-associated reduction in hematopoietic reserve.

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DIALOG(R)File 5:Biosis Previews(R)

0014410255 BIOSIS NO.: 200300368974
Use of the In Vitro Stem Cell Assay in Conjunction with Fluorescence In Situ Hybridization (FISH) To Detect Chromosomally Abnormal Leukemic Cells with Trisomy 8 in a Peripheral Blood Stem Cell Collection from a Patient in Complete Remission Prior to Autologous Stem Cell Transplant.
AUTHOR: Dodge William H (Reprint); Cruz Julia; Zamkoff Kenneth W; Hurd David D; Pettenati Mark J
AUTHOR ADDRESS: Pathology, Wake Forest University School of Medicine, Winston-Salem, NC, USA**USA
JOURNAL: Blood 100 (11): pAbstract No. 5490 November 16, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We report for the first time the use of FISH to detect the presence of chromosomally abnormal leukemic cells with trisomy 8 in an in vitro peripheral blood stem cell assay prior to transplant. An 18 year-old white male with no significant past medical history was diagnosed with acute myeloid leukemia, M5, associated with trisomy 8. His WBC at diagnosis was %17%,000 with a normal differential and platelet count of 58,000. The patient was induced into remission with chemotherapy with cytarabine and daunorubicin. At the time of morphologic remission, the bone marrow cytogenetics was normal showing no evidence of trisomy 8. He was next treated with high dose cytarabine and etoposide followed by administration of G-CSF daily and collection of autologous peripheral blood stem cells (PBSC) in preparation for high dose chemotherapy and autologous PBSC transplant. Prior to high dose chemotherapy and PBSC transplant his followup bone marrow showed normal trilineage maturation and no evidence of recurrent acute leukemia. An aliquot of PBSC was seeded at 10% by volume into Stem Cell Technologies Methocult GF H4434 medium. The cells were seeded into duplicate dishes at densities of 5.22 x104/dish and 1.31x104/dish and incubated at 37degreeC in 5% CO2. CFU-GM at 3.6 x104/kg and BFU-E at 2.4x104/kg were detected at day 14. No CFU-GEMM were detected. Since this patient was known to have trisomy 8, FISH analysis was used to analyze colonies with different morphological types. FISH identified the presence of a low incidence of trisomy 8 in cells from 3 of 4 tight GM colonies (3%, 2% and 2%, respectively) containing small, round, refractile cells. The incidence was significant in comparison to the laboratory's established sensitivity (99.6%) and the specificity (99.8%) detection rate for trisomy 8. Three disperse GM colonies containing small pleomorphic and round refractile cells did not have any +8 cells. As a result, the patient, early in first relapse, underwent a related matched allogeneic peripheral blood stem cell transplant from his sister. He has been in remission for 2 years. A repeat FISH analysis and an in vitro stem cell assay were performed 2 years later on QC vials of cryopreserved autologous PBSC from the patient's cells frozen in liquid nitrogen. One of two vials of uncultured cells was positive +8 while cultured dishes set up from each vial showed the presence of +8 cells. These results show that the in vitro stem cell assay in conjunction with FISH can be used to detect leukemic cells in PBSC derived from patients found to be in morphologic remission prior to transplant.

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DIALOG(R)File 5:Biosis Previews(R)

0014410248 BIOSIS NO.: 200300368967
Outcome of Hematopoietic Progenitor Cells Transplant in Patients with Acute Myelogenous Leukemia in First Complete Remission. Report from a Single Institution.
AUTHOR: Milone Gustavo (Reprint); Fernandez Isolda (Reprint); Rolon Juliana Martinez (Reprint); Corrado Claudia (Reprint); Pavlovsky Santiago (Reprint); Juni Mariana (Reprint)
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JOURNAL: Blood 100 (11): pAbstract No. 5483 November 16, 2002 2002
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We analyzed the outcome of 73 consecutive patients during June 1991 to June 2002 with acute myelogenous leukemia (AML) who underwent hematopoietic progenitor cells transplantation (PCT) in first complete remission. Adult pts received induction chemotherapy with Citarabine-Mitoxantrone (7/3), 1 or 2 cycles and a BFM-AML regimen in

children, all the pts received consolidation with Citarabine 12 gr/m 2 + Mitoxantrone 24 mg/m 2 x 1-4 courses followed by G-CSF 5 ug/Kg SC daily. Leukopheresis was performed when leukocytes reached 10x10 9/l. The ablative regimens were busulfan and cyclophosphamide (52 pts) and with etoposide (21 pts). The median age was 35 years old (2-65), and 12 pts (16%) were under 15 years; 33 (45%) were female and 40 (55%) were male pts. Distribution within the FAB classification was as follows: M0: 7 pts (10%), M1: 8 pts (11%), M2: 19 pts (26%), M3: 3 pts (4%), M4: 25 pts (34%), M5: 6 pts (9%), M6: 1 pts (1%), Biphenotypic: 4 pts (5%). The median of WBC at diagnosis was 10.0 x 109/l (1.0-690.0), only 4 pts had >100.000 x 109/l. According to the cytogenetics studies at time of diagnosis, the risk groups were: favorable 5 pts (7%), intermediate 22 pts (30%), unfavorable 20 pts (%28%%), not evaluable 9 pts (12%) and not done in %17% pts (23%). Two courses of induction therapy were needed to achieved CR in 10 pts (14%), and 30% received 2 or more courses of consolidation therapy before autograft. The median interval of time between diagnosis and time of transplant was 5 months (3-14). Sixty two pts received peripheral blood progenitor cells (PBPC) and 11 pts PBPC plus bone marrow. The median time to achieved ANC >1.0x109/l was 12 days (8-54); 80% of the pts recovered > 25.0x109/l platelets counts in a median time of 30 days (8-364). Treatment related mortality (TRM) was 8% (6 pts): sepsis 3 pts, CMV 2 pts and CNS bleeding in 1 pt. Thirty five out of 73 pts (47%) were alive and in continuous complete remission for a median of 83 months (1-130); 33 (45 %) pts relapsed. Five pts are alive after relapse, two of them in 2CR after allotransplant. The probabilities of event free survival and overall survival at 5 years were 47% and 54% respectively. We analyzed the prognostic factors that are associated with favorable long-term outcome. Patients less or equal 50 years of age (53 pts) had a better outcome than > 50 years old (20 pts) (EFS= 59% vs 18%, $p < 0.001$; OS= 65% vs 20%, $p < 0.001$). No statistical differences in event free survival and overall survival was observed according to WBC at diagnosis, FAB clasification, cytogenetic prognostic group, number of induction or consolidation cycles. In summary, our retrospective non randomized analysis shows that 47 % of selected adult pts with AML in 1CR can obtain a long-term benefit with high dose chemotherapy and autologous PCT.

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DIALOG(R)File 5:Biosis Previews(R)

0014410247 BIOSIS NO.: 200300368966
Continuous Infusion Idarubicin and Oral Busulphan as Conditioning for Patients with Acute Myeloid Leukemia Undergoing Autologous Stem cell Transplantation.
AUTHOR: Ferrara Felicetto (Reprint); Palmieri Salvatore (Reprint); Schiavone Ettore M (Reprint); Annunziata Mario (Reprint); Simone Mariacarla De (Reprint); Pocali Barbara (Reprint); Copia Carolina (Reprint); Mele Giuseppina (Reprint)
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JOURNAL: Blood 100 (11): pAbstract No. 5482 November 16, 2002 2002
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LANGUAGE: English

ABSTRACT: Autologous stem cell transplantation (ASCT) is an attractive option for acute myeloid leukemia (AML) in first or subsequent complete remission (CR). However, following ASCT 30-50% of patients still relapse. We previously demonstrated the feasibility of an original conditioning regimen, called IBu, consisting of high dose Idarubicin (IDA) administered at 20 mg /m2 as continuous infusion for three days (day -13 to day -11) plus oral Busulphan (Bu) given at 4 mg/kg from day -5 to day -2. In patients aged more than 60 years, two days of IDA (-12 to -11) and three days of Bu (-4 to -2) were given. Patients with acute promyelocytic leukemia (APL) or with t(8;21), inv(16) and t(16;16) were excluded when in CR1. Between June 1999 and March 2002, 35 patients were conditioned to ASCT with IBu regimen. 29 patients (83%) were autografted in CR1, 6 (%17 %) in CR2 including 3 cases of APL, one of AML with t(8;21), one relapse after previous ASCT and one early relapse in a patient waiting for ASCT. Among patients autografted in CR1, 23 had normal karyotype, while 6 showed different chromosomal abnormalities. The median age was 50 years (range 16-71) and 7 patients (20%) were aged over 60. All transplants were performed using peripheral blood stem cells (PBSC) collected after consolidation treatment followed by G-CSF. The median interval between CR achievement and ASCT was 2 months (1-4). The median number of CD34+ cells infused was 6,1 x 10E6/kg (2.6-16). In all patients left ventricular ejection fraction (LVEF) was evaluated before and after ASCT. The median number of days with granulocytes <500/cmm and of platelets <20000/cmm was 10 (7-21) and 13 (9-95), respectively. The median number of platelet and blood units transfused was 3 (1-7) and 3 (0-14), respectively. Extra-hematological toxicity included grade WHO III-IV stomatitis in 31 patients (89%). Total parenteral nutrition was required in 23 cases (66%), while 10 (%28%%) needed narcotic analgesics. One patient had grade III hepatic toxicity, consisting of increase of serum bilirubin and transaminases. Thirty-one patients experienced FUO, while 2 had documented fungal infection (1 hepato-splenic candidiasis and 1 pulmonary aspergillosis), both resolved with amphotericin B at the time of hematopoietic recovery. LVEF examination post-ASCT did not reveal cardiac toxicity in any patient. The median number of days of intravenous antibiotic therapy was 14 (7-50), the median time of hospitalization was 30 days (26-67). Eight patients (23%) needed empiric antifungal therapy. No patient died from transplant related mortality. After a median follow up of 12 months from transplantation, 27 patients are alive in continuous CR, while 8 have relapsed at a median time from ASCT of 7 months (4-12). Among relapsing patients, 6 received salvage therapy and 2 of them achieved CR2. Median disease free survival from CR achievement has not yet been reached after a median follow up of 12 months. In conclusion, in a series of AML patients with a median age of 50 years and not including those with favorable cytogenetics in CR1, our data demonstrate that IBu regimen is effective and well-tolerated. In particular, data concerning the reduction of relapse rate are extremely encouraging, but need to be confirmed in a larger series with longer follow-up.

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DIALOG(R)File 5:Biosis Previews(R)

0014410244 BIOSIS NO.: 200300368963
Treatment of Children and Adolescents with Juvenile Rheumatoid Arthritis (JRA) and Severe Systemic Lupus Erythematodes (SLE) with High Dose Chemotherapy and Autologous Stem Cell Transplantation (ASCT).
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ABSTRACT: ASCT has been proposed as a new therapeutic option for patients with severe autoimmune disease refractory to conventional treatment. Here, we report three children with a severe form of systemic JRA and two patients with severe systemic lupus erythematodes treated with ASCT in a phase I study. Patients: Three patients (age: 5, 9, 14 yrs) who developed

severe systemic JRA with high spiking fever, rashes, hepatomegaly, polyarthritis, morning stiffness, ESR > 100 mm/h, CRP > 100 mg/l were refractory to NSAIDs, MTX, cyclophosphamide, steroids, etanercept after 2.5, 13 and 6 yrs. 2 patients (age: 16, 20 yrs) with SLE had a disease duration of 2.5 / 5.5 yrs with arthritis, carditis, pericarditis, hypertonus, reduced pulmonary capacity, increased Anti-ds DNA titre. SLE was refractory to steroids, MTX, IVIG, CsA and cyclophosphamide (total doses: TPN 340: 14,2 g/m2; TPN 373: 6,2 g/m2). TPN 373 had a WHO class IV glomerulonephritis with a creatinine clearance of 52 ml/min nonresponsive to i.v. cyclophosphamide. Stem cell harvest: After a priming dose of cyclophosphamide (2-3 g/m2) and mobilization with G-CSF (10 mug/kg/day) peripheral blood stem cells were collected using of a Cobe separator. Using a Clinimacs device, CD34-positive selection was performed yielding a final CD34+ -cell amount of 4.2 - 11.9 x 106/kg contaminated with zero to 3.2 x 104/kg CD3+ lymphocytes, respectively. Stem cells were stored in liquid nitrogen. Conditioning regimen: Fludarabine (30 mg/m2): days -7 and -6; cyclophosphamide (50 mg/kg): days -5 to -2; ATG (5 -10 mg/kg): days -6 to -2; methylprednisolone (1g/m2): days -4 to -2. On day 0, the frozen CD34+ cells were thawed and infused. Results: All drugs but prednisolone were stopped before ASCT. Prednisolone was tapered and stopped 2 months after transplant. The conditioning of the patients with cyclophosphamide and G-CSF for CD34+ mobilisation was well tolerated without symptoms of reactivation of rheumatic arthritis and SLE. Rapid engraftment of neutrophils > 1.0 GPT/l: days +10 to +13; platelets > 20 GPT/l: days +6 to +19. Lymphocytes showed a tendency of normalisation during 5 months posttransplant in patients with JRA. One patient with SLE acquired on day + 45 EBV infection with LPD which was treated successfully with ganciclovir, cidofovir and rituximab. Patients were discharged from hospital on day + 24 to + 53 and remained free from active JRA and SLE with no immunosuppressive medication for 4, %17%, 19, 29 and 29 months, respectively. CHAQ score showed a clear improvement at evaluation 6-12 months after ASCT. The SLEDAI scores decreased continuously (TPN 340: day +365: 0; TPN 373: day +115: 4). After a traumatic injury one patient with JRA developed a gonarthritis %17% months after ASCT without symptoms of her initial disease as spiking fever, rash, morning stiffness. Conclusion: ASCT is a possible new approach that offers hope to such patients.

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DIALOG(R)File 5:Biosis Previews(R)

0014410242 BIOSIS NO.: 200300368961
High-Dose Chemotherapy (HDC) and Peripheral Blood Stem Cell Transplantation (PBSCT) Prolongs Survival in Previously Untreated Patients with Advanced Stage Multiple Myeloma (MM).
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ABSTRACT: To investigate the impact of HDC and autologous PBSCT on survival in patients (pts) with advanced stage MM, a prospective study using sequential double cycles (SDC) of HD cyclophosphamide (HDCY) and HD melphalan (HDMP) was performed and the results were compared to those of conventional-dose chemotherapy (CDC) in a historical control group of pts. From February 1994 to January 2000, 41 previously untreated pts received SDC of HDCY (3 g/m2, d1,2) and HDMP (100 mg/m2, d1,2) after treatment with a median number of 3 cycles of HD dexamethasone (DM) (n=21) or CDC (n=20). In 6 pts, 1 cycle of HDCY was given, in 32 pts 2 cycles, and in 3 pts 3 cycles. The number of HDMP cycles applied were 0 in 9 pts, 1 in 8 pts, and 2 in 24 pts. HDCY was supported by G-CSF or GM-CSF and HDMP by autologous PBSC, collected after HDCY cycles. Myeloma response before HD treatment consisted of partial remission (PR) in 68% of pts, no change (NC) in 25%, and progressive disease in 7%. After HD treatment, complete remission (CR), defined as disappearance of myeloma protein as indicated by immunofixation, and <5% myeloma cells in the bone marrow, was achieved in 46% (19/41) of pts, PR in 49%, and NC in 5%. The survival data of the whole group of pts were compared to those in a group of 41 pts, treated between December 1983 and April 1994, exclusively receiving CDC, with MP plus prednisone (n=31), an anthracycline-containing regimen (n=7) or DM (n=1) as initial treatment. The two groups were comparable with regard to age (median 49 and range 31-64 yrs in HD group versus 52 and 35-60 yrs, respectively, in CD group), sex (females/males 22/19 vs %17%/24) and stage of disease (I/II/III 1/7/33 vs 0/9/32). With a median follow-up of 30 months, median survival has not yet been reached in pts with HDCT and there is a probability of survival of 67% at 5 yrs, while pts with CDC showed a median survival of 32 months and a 5-yr-survival probability of 36% (p< .02). Based on these data, HDCT with SDC of HDCY and HDMP appears to be highly effective in inducing remissions in advanced stage MM and to be associated with significant advantage in survival compared to CDC.

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DIALOG(R)File 5:Biosis Previews(R)

0014410228 BIOSIS NO.: 200300368947
Successful Salvage with High-Dose Sequential Chemotherapy Coupled with Autologous PBSCT and In Vivo Purging with Rituximab in Patients with Primary Refractory Mantle Cell Lymphoma Presenting in Leukemic Phase.
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ABSTRACT: Although mantle cell lymphoma (MCL) shows an indolent histology, an aggressive clinical course is not uncommon. The long term-prognosis is poor with moderate sensitivity to chemotherapy and cure cannot be reached with conventional chemotherapy. Standard salvage regimens are not successful in inducing long-term remissions. We present two patients with MCL in leukemic phase, refractory to conventional therapies consisting of CHOP and IIVP (idarubicin, etoposide, ifosfamide) in patient-1 and chlorambucil+prednisone and COP in patient-2. The first patient presented with massive splenomegaly, bone marrow involvement and high WBC (111,000), while the second patient presented with generalised adenopathy and high WBC (30,100). Salvage therapy consisted of 4 phases: Phase I, debulking chemotherapy; phase II, immunotherapy; phase III, stem cell mobilization and in vivo purging with rituximab; and phase IV, high dose chemotherapy and autologous peripheral blood stem cell transplantation (PBSCT) followed by two consolidation doses of rituximab to treat minimal residual disease. Following phase I, a gallium negative CR was achieved in patient -1, while a good PR was achieved in patient -2.Mobilization failure which was thought to be related to previous fludarabine exposure was observed in patient-1. A second collection with G-CSF was successful. CD34+ cell dose infused per kg of body weight were 13,2 x 106 and 2,1 x 106, while myeloid engraftment was achieved on days +%17% and +10, respectively. Patients are in CR at 29+ and 33+ months. The therapeutic

approach summarized above appears to be tolerable and effective in high risk, primary refractory patients with MCL presenting in leukemic phase.

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DIALOG(R)File 5:Biosis Previews(R)

0014410227 BIOSIS NO.: 200300368946
High-Dose Sequential Chemotherapy in Relapsed or Refractory Hodgkin's and Non-Hodgkin's Lymphoma.
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ABSTRACT: The management of relapsed or refractory Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) is usually disappointing and long term survival is less than %10 with conventional salvage therapies. High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (APBCST) is widely used to achieve long term survival in such patients. From 2000 to 2002, 30 patients with relapsed/refractory HD or NHL with a median age of 40 years (M:F=24:6) were treated with high-dose sequential chemotherapy (HDSC) and APBSCT. Following 2 to 3 cycles of salvage therapy, chemosensitive patients were treated with HDSC/APBSCT. Phase I consisted of cyclophosphamide (4.5 g/m2) followed by G-CSF (10 mug/kg/d) and PBSC collection. Phase II consisted of etoposide (2 g/m2) with G-CSF support of at 5 mug/kg/d. The transplant phase consisted of mitoxantrone (60 mg/m2) and melphalan (180 mg/m2) followed by APBSC infusion. NHL patients had diffuse large cell (n=12), anaplastic large cell (n=2), mantle cell (n=2), small lymphocytic (n=2) and peripheral T cell (n=1) histology. Patients with HD had mixed cellular (n=7) and nodular sclerosing (n=4) histology. Seventeen (56.7%) patients had received prior radiation therapy, and 14 (46.7%) patients had failed two or more chemotherapy regimens prior to their salvage regimens. Prior to HDSC, %17% patients were in CR and 13 patients were in PR. Patients received a median of 5.3x106/kg CD34+ cells. Median times to achieve neutrophil and platelet engraftments were 14 and %17% days, respectively, with a transplant related mortality rate of 10% (n=3). Causes of mortality were; veno-occlusive disease (n=1), sepsis (n=2) and poor graft function (n=1). Three patients developed mild congestive heart failure, mainly due to high cumulative doses of antracyclines during their previous therapies. At 24 months, 25 of 30 transplant recipients are alive, 22 without disease (3 patients relapsed) with a median follow-up of 12 months. The estimated 2-year disease-free survival and overall survival are %90 and 81%, respectively. Regarding overall survival, there is no statistically significant difference between HD (77.8%) and NHL (82.5%), or between patients receiving one (85%) and more prior (75%) regimen in the univariate analysis. In conclusion, HDSC followed by APBSCT is an effective therapy in patients with relapsed/refractory NHL or HD, with an acceptable mortality rate.

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DIALOG(R)File 5:Biosis Previews(R)

0014410194 BIOSIS NO.: 200300368913
Adult Haplo-Identical Transplants: Hazards and Benefits of DLI and of the Type of Post-Transplant Growth Factor (G-CSF vs GM-CSF).
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ABSTRACT: Haplo-identical transplant is becoming a procedure of choice for patients who lack a compatible donor. However, they are still referred heavily pre-treated, at very advanced stages. This results in very high risk of relapse and infections. We therefore started a two-step DLI dose finding study to improve both relapse rate and immunity (the second step being the replacement of G-CSF by GM-CSF post-transplant). Seventeen consecutive leukemia patients were investigated (primary refractory: 4, refractory relapse: 7, CML 2nd CP progressive on STI: 2, early relapse in PR: 3 and CR: 1). A donor with GvH type NK alloreactivity was chosen when possible (9/%17%). Conditioning consisted of TBI, melphalan, ATG, fludarabine and CSA pre-transplant. In 4 progressive patients, Ara-C 2x1 gr/m2 for 2 days was added. The graft was T and B-cell depleted with a fixed reinfused CD3 dose of 5x104/kg. All but one patients engrafted before day 20. In the first 8 patients, G-CSF was given from day 5. The rule for discontinuing a given lymphocyte dose was two aGVHD grade II or more. Prophylactic DLI started at month 1 (3x104 CD3/kg) in the 2 first patients. This resulted in grade II aGVHD in both and in prolonged CSA-prednisone treatment in one. We gave next 1x104/kg monthly for 3 consecutive months. This was well tolerated with only one grade I GVHD. Overall, 5 patients relapsed rapidly (before month 6) and were given therapeutic DLI, starting at 1x105 CD3/kg with escalation every 2 weeks if no GVHD. This led to CR in 1/5. We next gave monthly escalated (1, 3 and 10x104) doses in bad risk patients. This produced cutaneous grade III aGVHD in one, resolutive on prednisone 1 mg/kg that is now tapered. We conclude that G-CSF from day 5 and prophylactic DLI are safe at a monthly dose of 1x104 CD3/kg. They results in faster CD4 recovery and a low rate of infections. However, in refractory diseases, this remains insufficient to induce a protective GVL effect. Therapeutic DLI can be given at higher doses, depending on the timing: 1x105/kg producing GVHD when given during the first two months, while doses up to 5x105/kg have been given without GVHD for relapse occurring after day 100. In the next 9 patients, GM-CSF was used first from day 1 plus monthly DLI (grade II GVHD in 2 patients), next from day 5 plus DLI. This produced either no GVHD or Grade I GVHD (4). Overall, TRM was 2/%17% at day 100 (one graft failure and one septicemia), 3/%17% at one year (infectious complication of GVHD) and 5/ %17% in total (CR patients with late exacerbation of GVHD with infectious complications). RRM occurred in 6 patients, which can be considered good in such a cohort, and 6 patients are alive in CR. It is worth noticing that among patients developing any grade of aGVHD post DLI, the relapse rate was 2/9 suggesting a protective effect, even with grade I. However, the price to pay is high for GVHD greater than grade I (3 deaths). We are thus aiming at a scheme producing no or grade I GVHD, which could be achieved with GM-CSF. We conclude that DLI are feasible in this cohort of patients, that GM-CSF plus one DLI tends to produce more GVHD, essentially type I when given from day 5, and that even grade I GVHD could be protective (a longer follow-up is needed)

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DIALOG(R)File 5:Biosis Previews(R)

0014410192 BIOSIS NO.: 200300368911
Outcome of Cord Blood Transplantation for Leukemia and Thalassemia in Hochiminh City, Vietnam.
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ABSTRACT: Bone marrow transplantation from unrelated donors is limited by lack of HLA-matched donors and risk of graft-versus-disease (GVHD). Cord blood from related and unrelated donors can reconstitute hematopoiesis. Between January and July 2002, We performed the first 5 cases of cord blood transplantation (CBT) at Blood Transfusion and Hematology Center: 1 case of HLA-identical sibling CBT and 4 cases of HLA-mismatched unrelated CBT (3 cases had 2 HLA differences and 1 case 3 HLA differences).The diagnosis was chronic myeloid leukemia in CP (n=1), acute myeloid leukemia in CR1 (n=1), acute lymphoblastic leukemia in CR1 (n=1) and beta- thalassemia (n=2). There were 3 females and 2 males. The median age at transplantation was 11 years (range 5-15 years) and median weight was 33kg (range 26.5-44 kg). Cord blood was provided by Hochiminh cord blood bank in 1 case and by Tokyo cord blood bank in 4 cases. The preparative regimen was Bu/Cy2 (busulfan 16mg/kg and cyclophosphamide 120mg/kg). The median dose of mononuclear cells, CD 34+ cells and CFU-GM was 3.1x107/kg (range 2-4.6x107/kg), 0.95x105/kg (range 0.34-1.75 x105/kg) and 5.3x104/kg (range 0.%28%-11.25 x 104/kg) respectively. Cells were thawed but not washed prior to infusion. GVHD prophylaxis consisted of cyclosporine and methotrexate. Cytomegalovirus prophylaxis consisted of gancyclovir and acyclovir. G-CSF (10mug/kg/day) was given during the nadir period until absolute neutrophil count (ANC) >2.x109/l for 3 consecutive days, At the time of report, 4 patients were evaluated for engraftment. The median time to recover ANC >0.5x109/l was 26 days (range 21-37 days) and the median time to recover platelet >20x109/l was 59 days (range 29-87days). Acute GVHD (grade I) occurred in 1 patient. These data suggest that cord blood is an alternative source of hematopoietic stem cells for allogeneic transplantation in children.

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DIALOG(R)File 5:Biosis Previews(R)

0014410163 BIOSIS NO.: 200300368882
Allogeneic Stem Cell Transplantation with Fludarabine Melphalan and Campath Conditioning for Adults with Advanced Sickle Cell Disease.
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ABSTRACT: We previously reported allogeneic transplantation using an attenuated conditioning regimen for two adults with advanced sickle cell disease. Although both patients engrafted promptly and with minimal regimen related toxicity, they both succumbed to complications of graft versus host disease.(van Besien et al, BMT, 26, 445, 2000) The protocol was subsequently modified to minimize the risk of GVHD. We report experience with 2 additional patients. The first patient was a 19 year old female with SS disease, a history of multiple episodes of chest syndrome and decreased pulmonary function tests. Conditioning consisted of fludarabine 120 mg/m2 and melphalan 140 mg/m2. This was followed by infusion of G-CSF mobilized blood stem cells from an HLA-identical sibling. Campath 1H 20 mg was added to the stem cells prior to infusion. No additional immunosuppression was given. Treatment related morbidity was minimal. The patient recovered donor hematopoiesis by day 15. The graft was completely rejected by day %28%. The patient then received an infusion of previously collected autologous blood stem cells and recovered autologous blood production approximately 10 days later. The second patient was a 24 year old patient with SS disease, a history of multiple pain crises, aseptic hip necrosis and multiple transfusions resulting in iron overload and transfusion induced antibodies. Conditioning consisted of fludarabine 120 mg/m2, melphalan 140 mg/m2 and campath-1H 20 mg daily x five days. This was followed by infusion of bone marrow and cord stem cells from her HLA-identical daughter. Post-transplant GVHD prophylaxis consisted of tacrolimus and mycophenolate mofetil. Regimen related toxicity was minimal. At 146 days after transplant, the patient's blood group has completely reverted to donor type and there are no sickle cells. There is stable 30-35% sickle cell hemoglobin consistent with sickle cell trait. PB chimerism studies indicate stable 50%-60% donor hematopoiesis. The patient has no evidence of GVHD and pre-transplant RBC antibodies have disappeared. These data indicate that the fludarabine-melphalan-campath regimen is well tolerated in adults with advanced sickle cell disease. One out of 2 patients achieved stable mixed chimerism with no detectable host erythropoiesis and without evidence of GVHD. Pre-existing transfusion related antibodies have disappeared.

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DIALOG(R)File 5:Biosis Previews(R)

0014410117 BIOSIS NO.: 200300368836
Tacrolimus and Mycophenolate Mofetil Are Superior to Cyclosporine and Methotrexate for GVHD Prevention after HLA-Matched Related Donor Hematopoietic Cell Transplantation.
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ABSTRACT: Preliminary data suggests a good safety profile and a low incidence of severe acute GVHD using tacrolimus (Tac) and mycophenolate mofetil (MMF) for GVHD prevention in hematopoietic allograft recipients (McSweeney et al, Exp Hematol 2002, 30:119). The purpose of this study was to compare acute GVHD and early transplant toxicities in recipients of Tac/MMF and cyclosporine (CSA)/methotrexate (MTX) as GVHD prophylaxis for conventional allografting. Methods: The first twenty-three patients (pts) with hematologic malignancy participating in an ongoing prospective phase II trial of GVHD prevention using Tac/MMF, who underwent allografting from HLA-matched related donors between June 2001 and March 2002 were analyzed. The median age was 40 years (range, 19-57). Regimens were cyclophosphamide/TBI (n=22) or busulfan/cyclophosphamide (n=1) and all received unmanipulated G-CSF mobilized blood stem cells. The median infused CD34 cell dose was 4.03 x 106/kg (range, 3.01-21.1). Tac 0.03 mg/kg i.v. was given by continuous infusion with target levels of 8-12 ng/ml, conversion at a 4:1 ratio for oral therapy and tapering between 2

and 6 months. MMF 15 mg/kg b.i.d. was given intravenously, then orally until day +%28%. G-CSF was given in 20/23 pts post-transplant until neutrophil recovery. Outcomes were compared to a control group (n=23) of pts who received myeloablative transplants at the University of Nebraska between April 1996 and February 2001. All controls received HLA-matched sibling donor PBSC transplants using identical GVHD prophylaxis of CSA (target levels 200-300 ng/mL) and MTX at 5 mg/m2 i.v. on days 1,3,6, and 11, with post-transplant G-CSF (10 mug/kg). CSA was tapered between 3 and 6 months. Matching criteria for selection of controls used those with known predictive value for acute GVHD: CD34 cell dose (<or> than 8x 106/kg), donor gender, CMV status, preparative regimen and age. Results: The median follow-up of study patients is 6 mo (range, 4-12), and of controls is 52 mo (range 16-67). At 100 days post-transplant cumulative incidence of acute GVHD grades II-IV and III-IV in Tac/MMF vs. CSA/MTX groups were 15% vs. 62% (p=0.0003) and 6% vs. 25% (p=0.025) respectively. Median time of engraftment for neutrophils (>500/muL) and platelets (>20,000/muL) in the study vs. controls were 10 vs. 15 days (p=0.001) and 13 vs. 19 days (p=0.11) respectively. There was no significant difference between the cases and controls in their mean maximum creatinine (mg/dL) during first 100 days post-transplant, 1.9 (SD 0.6), vs. 2.1 (SD 0.7), p=0.42. Day 100 survivals in Tac/MMF vs. CSA/MTX groups were 96% (CI:88-100%) vs. 78% (CI:60-96%) respectively, (p=0.10). Six-month cumulative incidences of any stage chronic GVHD were not significantly different, 21% vs 33% respectively (p=0.71). Six-month cumulative incidences of relapse in Tac/MMF vs. CSA/MTX were 13% vs. 4% respectively (p=0.56). Overall survivals at 6 months post-transplant were identical - in both groups at 78%. Conclusions: This analysis suggests that GVHD prophylaxis with Tac/MMF shows a lower incidence of acute GVHD, faster engraftment, and better safety profile than CSA/low-dose MTX in matched related-donor allogeneic blood stem cell transplants.

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DIALOG(R)File 5:Biosis Previews(R)

0014410109 BIOSIS NO.: 200300368828
Foscarnet Therapy for Patients with Cytomegalovirus Infection Undergoing Allogeneic Stem Cell Transplantation: Case Report.
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ABSTRACT: Introduction Cytomegalovirus (CMV) disease is often fatal in patients undergoing allogeneic stem cell transplantation (SCT). Because ganciclovir causes myelosuppression, it is difficult to use immediately after transplantation until engraftment. Foscarnet causes little myelosuppression, and has been reported to be useful as preventive therapy for CMV infection immediately after transplantation in high-risk patients. We report two patients who developed CMV infection before transplantation and received prophylactic foscarnet therapy until engraftment. Definitions and Methods CMV infection was defined as positive CMV antigenemia or positive CMV-PCR of the blood twice in succession with a one-week interval between tests. CMV disease was classified as interstitial pneumonia (IP), retinitis, and gastroenteritis. CMV antigen (Ag) and CMV-PCR were tested once a week. Foscarnet was administered at a dose of 60 mg/kg b.i.d. until day 30 after transplantation and then at 60 mg/kg 5 days/week from day 31 to day 100. The dose was adjusted in accordance with renal function. G-CSF support was also provided after transplantation. Case 1: On December 6, 2001, a 52-year-old woman with acute myelogenous leukemia (AML) underwent SCT from a one haplo-identical donor with conditioning Flu-Bu-ATG. CsA and MMF were used for immunosuppression, but graft rejection occurred on day 60. The white blood cell count was below 100/muL. CMV Ag testing was not possible, but the blood CMV-PCR remained positive when ganciclovir was administered. On April 5, 2002, second unrelated bone marrow transplantation was performed because of aplasia with conditioning Flu:Bu:TBI (4 Gy) was administered. CsA alone was used for GVHD prophylaxis. Granulocyte engraftment was achieved on day %17% and the CMV-PCR became negative on day 32. No CMV disease occurred and the only adverse reaction was mild renal dysfunction. Case 2: A 72 year-old woman had refractory ATL. CMV was present and the patient had been treated with ganciclovir, although CMV Ag did not become negative. Foscarnet was administered and CMV Ag became negative. Related PBSCT was performed on May %28%, 2002 with conditioning Flu-Mel. CsA alone was used for GVHD prophylaxis. Granulocyte engraftment was achieved on day 13. CMV Ag was positive only once after transplantation (on day 13), and no CMV infection or disease was observed thereafter. Conclusion Foscarnet had an adequate preventive and therapeutic effect on CMV infection when transplantation was performed in patients with prior CMV infection and did not interfere with bone marrow engraftment.

1/7/154
DIALOG(R)File 5:Biosis Previews(R)

0014410062 BIOSIS NO.: 200300368781
Regimen-Related Toxicity (RRT) Following Reduced-Intensity Hematopoietic Stem-Cell Transplantation (RIST): Comparison of Bearman's Criteria and NCI-CTC Version 2.0.
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ABSTRACT: Objective: The primary goal of this study was to evaluate the severity of RRT following RIST. The secondary goal was to compare the value of Bearman's criteria and the National Cancer Institute-Common Cancer Criteria version 2.0 (NCI-CTC) for predicting the development of RRT after RIST. Methods: The medical records of 86 patients who underwent RIST for the treatment of hematological diseases or solid tumors between September 1999 and April 2002 were reviewed. Preparative regimens included fludarabine 30 mg/m(2)/d or cladribine 0.11 mg/m(2)/d on days -8 to -3 and busulfan 4 mg/kg/d on days -6 and -5, with or without anti-thymoglobulin. Stem cell sources were G-CSF-mobilized peripheral blood from an HLA-identical sibling (n=64) or a one-locus-mismatched related donor (n=%17%), or bone marrow from an unrelated donor (n=5). GVHD prophylaxis consisted of cyclosporine alone (n=83) or a combination of cyclosporine and short-term methotrexate (n=3). Toxicity was graded using two systems, Bearman's criteria and NCI-CTC version 2.0, from the day conditioning regimens were initiated until 30 days after transplantation. Pulmonary toxicity was re-graded on day 100. Results: Twelve of the 86 patients (14.0%) died of transplant-related mortality (TRM). According to Bearman's criteria, four (4.7%) developed grade III to IV RRT, two of whom died of TRM (Table 1). According to NCI-CTC, 43 patients (50%) developed grade III to IV toxicity, 11 of whom died of TRM (Table 1). Among the 12 patients who died of TRM, 2 showed a maximum

toxicity of grade III to IV by Bearman's criteria, while this value was 11 with NCI-CTC. There was a significant association between RRT evaluated by NCI-CTC and Bearman's criteria, and the ultimate prognosis (p=0.034 and 0.008, respectively). Conclusion: Since far less RRT was observed after RIST, compared to data reported after conventional HSCT, Bearman's criteria might not be sensitive enough to evaluate the toxicity of preparative regimens and the ultimate prognosis, compared to NCI-CTC.

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DIALOG(R)File 5:Biosis Previews(R)

0014410042 BIOSIS NO.: 200300368761
Hematopoietic Reconstitution after Allogeneic BMT Using G-CSF (Granocyte(R)) - Stimulated Donors Undergoing Conventional Bone Marrow Collection. A Study of %17% Patients.
AUTHOR: Ostronoff Mauricio (Reprint); Matias Carolina (Reprint); Matias Kleber (Reprint); Barros Adriana (Reprint); Almeida Paulo Tadeu (Reprint) ; Florencio Rodrigo (Reprint); Maior Ana Patricia Souto (Reprint); Calixto Rodolfo (Reprint); Domingues Mariana (Reprint); Queiroz Simone (Reprint); Sucupira Alexandre (Reprint); Tagliari Clemente (Reprint); Soussain Carole (Reprint)
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ABSTRACT: It is well established that G-CSF - mobilized peripheral blood progenitor cells (PBPC) harvests contain more CD34+ cells and patients achieve a more rapid engraftment. Some reports, however, have indicated that the risk of developing acute and chronic GVHD is higher, possibly because such PBPC harvests contain approximately 10 fold more T lymphocytes than BM. A few groups are trying to associate the faster engraftment of PBPC to the lower incidence of GVHD observed in BMT, using G-CSF - primed BM conventionaly harvested from iliac crests for allo BMT. Between January 2001 and June 2002, %17% patients underwent sibling matched BMT with G-CSF - stimulated BM cells. After signing an informed consent form, all donors received subcutaneous G-CSF (lenograstim - Granocyte(R)) 5 mcg/kg/day for 5 days (D-4 to D0). GVHD prophylaxis included cyclosporin from D-1 and methotrexate 15mg/SQm on D1 and 10mcg/SQm on days 3, 6 and 11. Patients received Granocyte(R) 10mcg/kg/day until hematological recovery. Patients were F:8 ; M: 9; CML - 8, SAA - 2, AML - 2, ALL - 2, MDS - 2, NPH - 1. Median age was 30 (9 - 49 years). The BM harvests contained a median of 3.8 x 106 CD34+ cells per kg (range, 1.1 - 13.5 x 106/kg). Median time to engraftment was 13 days (range, 8 - 20 days) to neutrophil and 23 days (10 - %28%) to platelets. One patient experienced engraftment failure probably due to immunological rejection (multiple previous blood transfusions or insufficient conditioning) and other died before platelet engraftment due to pulmonary Aspergillosis. Comparing these results with data in literature we found the median time to neutrophil engraftment in our study was much faster than unstimulated BM. Time to platelet engraftment, however, was similar to those observed in unstimulated BM harvests.

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DIALOG(R)File 5:Biosis Previews(R)

0014409994 BIOSIS NO.: 200300368713
Absence of Effect on Platelet Count of G-CSF Administration in Peripheral Blood Progenitor Cell (PBPC) Donors: A Single Center Experience.
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ABSTRACT: G-CSF is increasingly being given to healthy donors in order to mobilize and collect PBPC for allogeneic transplantation. For the donor, PBPC collection by apheresis has practical advantages over traditional marrow harvest and a growing amount of data on adverse events demonstrates that G-CSF has an acceptable short-term safety profile in the vast majority of normal people. However, several reports have pointed out platelet decrements following cytokine-facilitated PBPC harvests. In our center, previous studies have not confirmed such findings prompting us to analyze retrospectively our experience using G-CSF (filgrastim) at dose of 10 mcg/kg/day for 4 days in a consecutively series of 51 PBPC donors (%28% males/23 females, median age 29.5 years, range 8 to 67) following 55 mobilization procedures. Aphereses were performed with the continuous flow cell separator COBE-Spectra. In 40 out of the 55 procedures, a single apheresis was performed; the remaining cases underwent apheresis on two consecutive days. The median CD34+ cell dose collected was 330.14 X 10e6 (range, 86.60-2428). As previously reported, a significant rise of white blood cells count was observed following G-CSF administration: from 6.70 X 10e9/l (range, 4.18-12.36) to 45.10 X 10e9/l (range, 19.70-73.99) (p<0.001), and a slight but significant decrease of hemoglobin level was also evidenced: from 14.7 g/dl (range, 11.1-%17%.6) to 14.2 (range 10.9-16.6) (p<0.01). The platelet count was unchanged following G-CSF administration: the median platelet count was 209 X 10e9/l (range, 159-333) before treatment and 214 X 10e9/l (range, 144-412) after G-CSF administration (p=0.87). Following leukapheresis, both the hemoglobin level (median 13.4 g/dl; range, 10.0-16.6) and the platelet count (median 91 X 10e9/l; range, 27-245) showed significant decreases (p<0.001). The platelet count fell below 100 X 10e9/l and 50 X 10e9/l in 58.2% and 9.1% of the cases, respectively. Therefore, in our series the thrombocytopenia was clearly related to the apheresis procedure, particularly if two aphereses were performed or large volumes processed. In consequence, in healthy PBPC donors the administration of G-CSF at dose of 10 mcg/kg for 4 days does not cause significant platelet depletion and allows the collection of an acceptable progenitor cell dose with one leukapheresis procedure.

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DIALOG(R)File 5:Biosis Previews(R)

0014409985 BIOSIS NO.: 200300368704
G-CSF Schedule in the Mobilization of CD34+ Cells for Transplantation: Effectiveness of a Flexible Strategy.
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JOURNAL: Blood 100 (11): pAbstract No. 5220 November 16, 2002 2002
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LANGUAGE: English

ABSTRACT: The optimal strategy for mobilization of CD34+ cells is unknown. While schedules that include filgrastim at 10 ug/kg/day are commonly used, they have considerable side effects, may mobilise higher number of TH2 cells and are more expensive. We firstly undertook a retrospective analysis of the rate of myeloid recovery in 15 patients, who had received HLA allogeneic transplants with the numbers of CD34+ cells collected from their donors and based on these results, designed a flexible strategy in the dosing with G-CSF. Donors were pre-treated with G-CSF at 5 ug/kg/day for 5 days and stem cell harvests were undertaken on day 6 by large volume aphaeresis (>4 blood volumes) on Cobe Spectra systems for 1 or 2 consecutive days. The median donor blood CD34+ before initiating aphaeresis was 24.8 (range 7-93)/mL. Their median mononuclear cell number collected was 7.8 (range 5.37-9) 108/kg, containing a median of 1.15 (range 0.61-8) x 106/kg CD 34+ cells. Time to engraftment (polymorphs >0.5 and platelets >40 x109/L) was 12 (range 11->120) days. A significant correlation (gamma) between time to engraftment and the infused CD34+ x106 cell/kg (p=0.03) was seen. A strong correlation was found between collected CD34+ number and absolute blood CD34+ count on the day of the harvest (p=0.02). 3 patients developed graft failure and in all their donors were"poor mobilisers", who had donated a median of 0.64 (range 0.64-1) x106/kg CD34+ cells. Regression analysis showed that the strongest association with a successful collection (>x106/kg CD34+) was the pre-harvest blood CD34+ count (p=0.0004) with a cut off point at 22 x106/mL. 40% of donors failed to reach this level. Consequently, in them, G-CSF dose was increased to 10ug/kg/day starting on day 6. Blood stem cells were daily enumerated and harvests were commenced only when >21/mL CD34+ had been documented. Another 46 patients with a median age of 37 years (range 11-64) who received 64 stem cell collections were subsequently studied. On day 6 the median CD34+ count was 23/mL (range 2.58-108). %28% donors who exceeded the cut off figure had a median of 32 x106/kg (22.64-108) CD34 circulating cells and proceeded directly to aphaeresis. In %17% donors the count failed to reach this threshold cell number and they received a median of 1 day of G-CSF at 10 ug/kg. On day 7 all exceeded the target stem cell blood level achieving a median of 30/mL CD34+ cells (range 23-157.49). Among donors with CD34+ </>22/mL cells on day 6, female/male gender was 13/4 and 2/14, respectively (p= 0.0003). During aphaeresis, there was no difference in the proportion of CD34+ harvested at 15 liters (78.47 (%17%.05-267) vs 81.9 (%28%.1-503.4) x 106; p= 0.08) to that of the end of the collection (127.49 (79.6-332.98) vs. 184 (46-581.26) (p= 0.08) x 106; p= 0.07) between the 2 groups. Median time to engraftment was 11 and 10 (p= 0.3) days, respectively. None of the patients developed graft failure (p= 0.001 with previous study). We conclude that release of CD34+ cells appears to be constant and that females have a lower CD34+ cell number after 5 ug/kg G-CSF schedule, but all patients responded well to a one-day double dose G-CSF injection, that in 36 patients resulted in sufficient stem cells collected with only one aphaeresis. However, donors who failed to mobilize adequately on day 5 required significantly more collection procedures (5/12 vs 1/15; p= 0.03) to reach target stem cell numbers.

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DIALOG(R)File 5:Biosis Previews(R)

0014409949 BIOSIS NO.: 200300368668
The Accelerated Engraftment of Peripheral Blood Cell Counts Following Transplantation with Hematopoietic Stem and Progenitor Cells (HSCs) Mobilized by the CXC Chemokine GRObeta Is Independent of the Stromal Cell-Derived Factor-1alpha SDF-1alpha:CXCR4 Migration Axis.
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ABSTRACT: Mechanisms responsible for homing and engraftment of hematopoietic stem cells (HSCs) after transplantation are poorly understood. The chemokine receptor CXCR4 is expressed on primitive HSCs and its interaction with SDF-1alpha has been considered to play an important role in homing. We have reported that the CXC chemokine GRObeta (CXCL2) rapidly mobilizes HSCs into peripheral blood when used alone and synergizes with G-CSF when used in combination. We now demonstrate that hematopoietic engraftment, defined by restoration of absolute polymorphonuclear neutrophil (ANC) and platelet counts (PLT) occurs faster in mice transplanted with 2 x 106 peripheral blood mononuclear cells (PBMCs) mobilized by GRObeta (15 min post single administration of 2.5 mg/kg, SC) (Days to ANC>500 = 15, P<0.05; Days to 40/80% PLT recovery = 18/23, P<0.05) compared to G-CSF (50 ug/kg, bid, SC, x 4 days) (Days to ANC>500 = %17%, P<0.05; Days to 40/80% PLT recovery = 25/36, P<0.05) . ANC recovery was significantly improved in mice transplanted with PBMCs mobilized by the combination of GRObeta plus G-CSF (2.5 mg/kg GRObeta on day 5 post 4 day G-CSF regimen) (Days to ANC>500 = 12.5, P<0.05), although PLT recovery was slower than observed with GRObeta alone (Days to 40/80% PLT recovery = 20/29, P<0.05). The PBMC mobilized by GRObeta and G-CSF contained 229 +- 81 and 270 +- 39 CFU-GM and 102 +- 41 and 147 +- 47 CFU-GEMM respectively, indicating that acclelerated ANC and PLT recovery with GRObeta mobilized PBMC was unlikely due to increased numbers of transplated CFU. In contrast, PBMC mobilized by GRObeta plus G-CSF contained 1810 +- 340 CFU-GM and 681 +- 179 CFU-GEMM that likely contributed to accelerated hematologic recovery. Since in vitro migratory ability of peripheral blood CD34+ cells mobilized by G-CSF is associated with hematopoietic recovery, we examined the migration of mouse peripheral blood HSCs mobilized by GRObeta alone and in combination with G-CSF towards SDF-1alpha in transwell plates. Transmigration of CFU-GM in the c-kit+, lin- PBMC populations mobilized by GRObeta and the combination of GRObeta plus G-CSF to 100 ng/ml SDF-1alpha was significantly reduced (77.1 +- 3.2% and 68.0 +- 4.1%, respectively; P<0.001) compared to CFU-GM in the c-kit+, lin- PBMC population mobilized by G-CSF. Transmigration of CFU-GEMM was reduced by 82 +- 0.4% and 70.9 +- 6.1%. Reduced migration to SDF-1alpha was not due to change in CXCR4 expression, although a marginal decrease in CXCR4 (31 +- 2.4%) was observed on c-kit+, lin- PBMC mobilized by G-CSF plus GRObeta. Transmigration of GRObeta mobilized CFUs was also impaired when unseparated PBMCs were analyzed. Total CFU-GM and CFU-GEMM that migrated toward SDF1 in GRObeta mobilized blood was reduced by 62.6 +- 0.4% and 86.1 +- 3.5% compared to CFUs mobilized by G-CSF, respectively. These data suggest that the accelerated engraftment capability of HSCs mobilized by GRObeta compared to HSCs mobilized by G-CSF is not due to increased numbers of transplanted short term repopulating cells or associated with migratory potential to SDF-1alpha. Additional mechanisms, including cell cycle and adhesion molecules may be responsible and are under investigation.

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DIALOG(R)File 5:Biosis Previews(R)

0014409889 BIOSIS NO.: 200300368608
Peripheral Blood Stem Cell Collection (PBSC) after CAD Plus G-CSF in Multiple Myeloma: No Influence of Previous Thalidomide (Thal) Administration.
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JOURNAL: Blood 100 (11): pAbstract No. 5124 November 16, 2002 2002

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ABSTRACT: OBJECTIVES: It was previously reported that Thal induced remissions in 30-50% of refractory MM patients. Munshi et al. (Blood 1999, Abstract 2577) described a dampening of PBSC-mobilisation by Thal treatment. In a joint study of the GMMG and HOVON groups, induction therapy with Thal, doxorubicin and dexamethasone (TAD) is currently investigated in comparison with vincristin, doxorubicin and dexamethasone (VAD). METHODS: Altogether, data on 31 patients treated in our clinic were analyzed in terms of PBSC-mobilisation and side effects. %17% patients were randomized up-front to receive 3 cycles of TAD (Thal 400mg/d orally; doxorubicin 9mg/m2/d, 4 30-min. infusions, day 1-4; dexamethasone 480mg total dose orally). 14 patients received VAD (vincristin 0,4mg/d and doxorubicin 9mg/m2/d, 4 30-min. infusions, day 1-4.; dexamethasone 480mg total dose orally) followed by mobilisation with CAD (cyclophosphamide 1g/m2/d, 1h infusion, day 1; doxorubicin 15mg/m2/d, 4 short infusions, day 1-4; dexamethasone 160mg total dose orally) and G-CSF (Neupogen 600mug/d s.c. or Granocyte 526mug/d s.c., day 5 after the end of chemotherapy until PBSC). Thal was stopped two weeks before CAD. Low dose heparine was administered to prevent deep venous thromboses (DVT) in the TAD group. RESULTS: The median time was 14 days after the first day of CAD until PBSC in patients in both the TAD (range 12-18 days) and VAD group (range 10-19 days). In the first leukapheresis, a median total PBSC yield of 9,4x106/kg CD34+ cells in the TAD/CAD (range 2,3-30,8x106 CD34+ cells) and 9,9x106/kg CD34+ cells in the VAD/CAD (range 5-26,9x106 CD34+ cells) group could be harvested (p=0.82). There was also no difference between both groups in terms of best leukapheresis defined by the highest number of CD34+ cells/kg BW (p=0.82). 1 patient developed polyneuropathy (PNP, Grade III, WHO) so Thal was stopped. One patient had atrial fibrillation, Thal was stopped and resumed 1 week after spontaneous conversion. One DVT ocurred 10 weeks after treatment with Thal, a further thromboses was found in the TAD group after insertion of a port. One patient had pneumonia after 1 cycle of TAD. One patient developed DVT 8 weeks after the end of VAD treatment. Three patients had pneumonia, two of them 8 weeks after therapy started, one patient 2 weeks after the end of VAD treatment. CONCLUSIONS: No difference was found in stem cell collection and yield after TAD versus VAD. Furthermore, the number of thromboses during treatment with TAD seems to be low due to heparine administration.

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DIALOG(R)File 5:Biosis Previews(R)

0014409780 BIOSIS NO.: 200300368499
Fludarabine, Mitoxantrone and Cyclophosphamide Combination Therapy in Relapsed Chronic Lymphocytic Leukemia (CLL) with or without G-CSF: Results of the First Interim Ananlysis of a Phase III Study of the German CLL Study Group (GCLLSG).
AUTHOR: Schmitt Barbara F (Reprint); Franke Astrid; Burkhard O; Schlag R; Hopfinger Georg; Stauch M; Bergmann Manuela; Wendtner Clemens M; Busch Raymonde; Emmerich Bertold; Hallek Michael; GCLLSG
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ABSTRACT: Introduction: Fludarabine combination therapies are very effective regimen in treatment of relapsed CLL with overall response rates (ORR) of up to 90%. In a phase II study, FCM was shown to induce an ORR of 78% with 50% complete remissions in pretreated CLL (Bosch et al., 2001). However this regimen seems to cause a relatively high rate of severe infections. In a retrospective study the growth factor G-CSF was shown to reduce the rate of infections in fludarabine treated patients (pts) (O'Brien et al., 1997). Therefore the GCLLSG initiated the CLL 6 protocol, a phase III study, to evaluate the efficacy of FCM and the effect of G-CSF in relapsed CLL. Patients: Until 07/2002 63 pts with advanced (Binet stage B and C) and relapsed CLL were included in the CLL6 protocol. 31 pts were randomized to FCM (F 25mg/m2 day (d) 1-3, C 200mg/m2 d1-3, M 8mg/m2 d1, q %28% d) plus G-CSF (5 mug/kg bodyweight d 6 until neutrophil count increases after the nadir), 32 to FCM without G-CSF. 2 pts were not randomized and received G-CSF because of previous history of severe infections. Results: Relevant documentation from 32 pts (25 male and 7 female pts) was available. The median age was 62 years. Previous therapy and response to previous therapies is known in 19 pts: 11 pts (58%) had 2 or more previous therapies, 10 pts (53%) had received fludarabine before, 7 pts (37%) were refractory to previous therapy, 2 pts were even refractory to fludarabine therapy. So far 136 courses of chemotherapy were documented. Response to treatment was evaluable in 27 pts: 1 pt had a complete remission (CR), 20 pts had a partial remission (PR) and 6 pts stable disease (SD) or progressive disease (PD), resulting in an overall response rate of 77,8 %. So far 6 pts relapsed. The median relapse free survival time (RFS) was 18,2 months (mo). The main side effects in both arms were myelosuppression and infections. As expected, leukocytopenias were significantly more frequent in the arm without G-CSF (p = 0,00). No significant difference of the rate of severe infections was seen so far. Severe (common toxicity criteria (CTC) grade 3and grade4) thrombocytopenias and anemias were more frequent with G-CSF. Conclusion: FCM is a very effective regimen in the therapy of relapsed CLL. The main toxicities (myelosuppression) of this regimen is acceptable. Severe infections were observed only in 2 cases. So far there is no significant difference regarding the rate of infections when comparing the arms with and without G-CSF.

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DIALOG(R)File 5:Biosis Previews(R)

0014409770 BIOSIS NO.: 200300368489
Peripheral Blood Progenitor Cell Mobilisation in Chronic Lymphocytic Leukaemia Is More Difficult Than in Other Lymphoproliferative Disorders: Results of a Prospective Trial.
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LANGUAGE: English

ABSTRACT: Although it is possible to mobilise peripheral blood progenitor cells from patients with chronic lymphocytic leukaemia (CLL), much debate exists about the relative efficacy of the standard mobilising schedules in patients with CLL compared to patients with other lymphoproliferative disorders and multiple myeloma. In a prospective randomised trial designed to compare the mobilising efficiency of G-CSF (lenograstim 10mcg/kg) for 5 days versus cyclophosphamide (2g/m2) and G-CSF (lenograstim 5mcg/kg) for 7 days we also examined the ability to mobilise stem cells in patients with CLL compared to other lymphoproliferative

disorders. 22 patients with CLL and 57 patients with other lymphoproliferative disorders were studied during attempts at mobilising stem cells. A successful harvest, defined as greater than 2 x 106 CD34+ cells per kilogram body weight was achieved in 3/10 patients using cyclophosphamide + G-CSF and in 4/12 patients using G-CSF alone in the CLL group, giving a total success rate of 7/22 (31%). In the group with other lymphoproliferative disorders, a successful harvest was obtained in 19/29 patients with cyclophosphamide + G-CSF and in 24/%28% patients using G-CSF alone, giving a success rate of 43/57 (75%, p<0.003) No significant difference in terms of the adequacy of harvest was observed between the two mobilisation schedules in either group. A boxplot of the results is shown below. There has been anecdotal evidence for some time that progenitor cell mobilisation is more difficult in CLL than in other lymphoproliferative conditions. This is the first prospective study which clearly demonstrates this. The causes are not clear. The CLL patients had all received fludarabine, which may damage progenitor cells. None of the patients were mobilised within three months of fludarabine exposure. The patients with CLL all had bone marrow involvement with tumour at the time of mobilisation and this may also be a factor although in a separate study the degree of marrow infiltration with CLL was not a prognostic factor for successful mobilisation. Given the relative failure to harvest CLL cells with these regimens, a disease specific approach may be needed. Dexa-BEAM + G-CSF may be a more efficient schedule.

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DIALOG(R)File 5:Biosis Previews(R)

0014409510 BIOSIS NO.: 200300368229
Unexpected Hematotoxicity Associated with a Combination of Rituximab, Fludarabine and Cyclophosphamide in the Treatment of Relapsed Follicular Lymphoma.
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ABSTRACT: Background: Fludarabin (F) in combination with cyclophosphamide (C) is an effective combination in the treatment for newly diagnosed as well as relapsed follicular lymphoma (FL). The anti-CD20 antibody Rituximab (R) has been used for the same indications successfully as monotherapy or in combination with chemotherapeutic agents. No such data were available on a combined use of these agents. Therefore, we conducted a phase II study to evaluate the safety and efficacy of a combination of R, F and C for the treatment of relapsed FL. With Flu being a T-cell and R a B-cell toxic agent R infusions were limited to two cycles to avoid potentially excessive infectious complications. Methods: Patients (pts) received R 375mg/m2 day 1 (cohort A: cycle 1+2, cohort B: cycle 5+6, to test optimum time point (bulk reduction vs. MRD-treatment) for the use of R), C 750mg/m2 day 2 and F 25mg/m2 IV days 2-5 for a maximum of 6 cycles. Dosages for R, F and C corresponded to dosages employed in previous studies. Cycle interval was %28% days. Support therapy consisted of trimethoprim/sufametho-xasole and acyclovir (day 1-14 of ea. cycle or longer if leukopenia persisted), and G-CSF if prolonged granulocytopenia occurred. In a pilot phase 10 patients were treated in cohort A, thereafter, 7 more patients were randomized between cohort A and B. One pt was later excluded from the study after diagnosis was revised by the reference pathologist. One pt. underwent high-dose chemotherapy with autologous stem cell transplantation 6 weeks after the study treatment as consolidation treatment.. Response is summarized in table 1. Toxicity was assessed according to WHO criteria. Regarding infectious toxicity 1 pt developed bronchitis and zoster during therapy, 1 pt developed PCP-pneumonia 6 mo. post end of treatment and died. 2 pts died from progressive disease and infection 2 and 8 mo. post treatment. Beyond that, a significant hematotoxicity (namely thrombocytopenia) occurred. 2/ %17% pts showed thrombocytopenia (tcp) WHO grade III and 5/%17% pts grade IV. Therapy had to be terminated in 5 pts after 3,6 cycles (range 3-5)due to prolonged (> 1 mo.) tcp. Leukopenia occurred in 4/%17% pts (grade III) and 7/%17% (grade IV) and led to delays in therapy in 2 pts. 5/7 pts recovered from tcp after an average of 2,4 mo.(range 1-4 mo.), 2/7 pts showed persistent tcp, one pt received an autograft and recovered. Serologic investigations gave no evidence for an autoimmune process and bone marrow aspirations in pts with tcp pointed towards a direct toxic effect. The excessive hematotoxicity led to activation of a stopping rule and the study was terminated. Conclusions: R-FC is an effective regimen in pts with relapsed FL. Yet, combining R and FC at dosages that have been applied safely before for R and FC individually, led to an unexpected and significant increase in hematotoxicity.

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DIALOG(R)File 5:Biosis Previews(R)

0014409479 BIOSIS NO.: 200300368198
IIVP Salvage Regimen Induces High Response Rates in Patients with Relapsed HD or NHL Prior to Autologous HSCT.
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ABSTRACT: Patients with relapsed lymphoma can be cured with high-dose chemotherapy and autologous stem cell transplantation(HSCT), the standard treatment modality in this setting at present. Achieving maximal cytoreduction prior to HSCT is a crucial factor. Since only responders to the salvage regimen will be transplanted, chemosensitivity of the malignancy is the key issue and only half of the patients with relapsed lymphoma will adequately respond to widely used salvage regimens. We report 30 patients with relapsed lymphoma, median age 43 (19-65), treated with 66 cycles of IIVP regimen consisting of ifosfamide (1 g/m2X5d), mesna (600 mg/m2X5d), idarubicin (10 mg/m2X2d) and etoposide (150 mg/m2X3d) for 2 or 3 cycles, depending on the response achieved. Thirteen patients had Hodgkin's disease (HD), 11 had intermediate grade, 4 had high grade and 2 had low grade non-Hodgkin's lymphoma (NHL). Fourteen (48%) patients were at their first relapse, 6 (21%) at second and 7 (24%) were beyond their second relapse. Three had primary refractory disease. Overall response rate was 83 percent (n=25). Seventeen patients (59%) achieved CR and 8 patients (%28%%) achieved PR. Only 5 patients (%17%%) had no response. Of 14 cases with a positive gallium scan, 9 (64%) became negative. The overall response rate was 92% in patients with HD and 81% in patients with NHL. The most frequent side effects were grade III-IV neutropenia (87%) and thrombocytopenia (76%). High rate of neutropenic fevers observed in the first 23 patients treated necessitated upfront use of G-CSF in the remaining patients. Neutropenic fever was observed in 62% of patients without mortality. Leading to high response rates with reliable cytoreductive capacity demonstrated by negative gallium scans. Close follow-up is needed due to high incidence of grade III-IV hematological toxicity. IIVP regimen is a highly effective salvage therapy for patients with relapsed HD or NHL prior to autologous HSCT.

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DIALOG(R)File 5:Biosis Previews(R)

0014409475 BIOSIS NO.: 200300368194
Evaluation of Efficacy and Toxicity of Rituximab Plus Aracytin-Platinum (R-DHAP) Regimen in Non-Hodgkin Lymphoma (NHL) Relapsing Patients.
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ABSTRACT: Rituximab has been previously shown to improve the remission rate in combination with CHOP-like regimen in first line lymphoma treatment. A combination of Rituximab and DHAP was used in 20 NHL relapsing patients. There were 12 females, 8 males, with a median age of 54 (40-70)yr. Histology : 12 diffuse-large-B-cell, 4 small lymphocytic, 3 follicular, 1 mantle-cell lymphoma. 10 patients were in first relapse, 7 pts were in second relapse and 3 pts were in third relapse. 10 pts were treated with one single previous line of chemotherapy (1-4). None of patients previously received Rituximab. Two strata were considered. Stratum 1: 11 pts relapsing after Autologous Stem Cell Transplantation (ASCT). Stratum 2: 9 pts relapsing without ASCT. Hematological characteristics at relapse were : stages 3-4 : 16/20 ; ECOG 2-4: 2/20 ; LDH > NI : 7/20 ; extra-nodal site > 1 : 3/20. The distribution in the International Prognostic Index (IPI) was : IPI=0: 3/20 ; IPI=1: 5/20 ; IPI=2: 9/20 ; IPI= 3: 3/20. Patients received Rituximab on day 1 (13 pts) or on days 1 and 8 (7 pts) plus Aracytin-platin regimen (R-DHAP) every 3 weeks. G-CSF was given on day 6 during a 7 day period. 6 cycles/patient were planned. A total of 85 cycles were given; median number/patient was 4 (2-6). Patients received theoretical or reduced doses. For the first four cycles : median Platinum dose was 71.5% of the theoretical dose (50%-100%) in stratum 1 patients versus 100% (75%-100%) in stratum 2 patients and 60% (40%-80%) for Aracytin in stratum 1 patients versus 90% (35%-100%) in stratum 2 patients. The hematologic 3-4 grade toxicity was evaluated at each cycle : 53 % of pts presented a 3-4 grade toxicity for platelets, 25 % for leukocytes and 7% for hemoglobin. However, there was an increased toxicity on platelets for pts relapsing after ASCT (69.1% versus 36.4 %). The non-hematologic 3-4 grade toxicities were evaluated for each patient : nervous system (4/20), kidneys (9/20), auditory (3/20), nausea (9/20), constipation (4/20), serious infections (13/20), facial oedema: (1/20). There were 2 toxic deaths (neurological, pulmonary embolism). Overall response rate at the end of the treatment was %17%/20 (85 %) with 70% CR, median duration of response was 240 days with 10 months median follow-up. Details of response are given in table 1. Conclusion: R-DHAP is highly active in relapsing NHL and seems superior to historical DHAP. Severe toxicity was observed after ASCT despite doses reduction. Randomized comparisons of salvage regimen with Rituximab are warranted.

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DIALOG(R)File 5:Biosis Previews(R)

0014409472 BIOSIS NO.: 200300368191
Gemcitabine with Dexamethasone+/-Cisplatin in Patients with Relapsing/Refractory Mantle Cell Lymphoma.
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ABSTRACT: MCL is currently non curable and the optimal management of these mostly elderly patients remains to be defined.We have previously shown that single agent gemcitabine is active in patients with mantle cell lymphoma (MCL) (Dumontet et al., Br.J.Haematol., 2001,113:772).Gemcitabine demonstrates synergy with cisplatin in vitro.We designed a new regimen with gemcitabine and dexamethasone (DG), combined with cisplatin (PDG) in patients less than 70 years old, given on an outpatient basis. Between December 2000 and May 2002, 24 patients with refractory or relapsing MCL were enrolled on an open label, multicenter, phase 2 trial whose primary objective was to determine the overall response rate(ORR) after 3 to 6 cycles of DG /PDG.Twelve patients received DG: gemcitabine 1g/m2 on days 1 and 8 and dexamethasone 40 mg/day on days 1,2,8 and 9(recycling on day %28%). Twelve patients received the same protocol combined with cisplatin (100 mg/m2 on day 1) but with recycling on day 21(PDG). G-CSF and EPO support was allowed.The median age was 70 years (range: 47-80). Prior treatment included anthracyclines (n=18), cytarabine (n=9), cisplatin (n=7), rituximab (n=3)-containing regimens and intensive chemotherapy followed by autologous stem cell transplantation (n=6). Fifty percent of the patients had received at least 2 prior regimens (range: 1-4). The median time between first diagnosis and accrual was 31.5 months (range: 1-83). The median time between the end of prior treatment and PDG/DG was 13.1 months(range:1-68.5). 91 cycles were given. The median number of cycles was 6 for PDG (range :2-6) and 5 for DG(range:1-6). In patients treated with PDG, the doses of gemcitabine and ciplatin administered were 80% and 71% of the intended doses, respectively. In patients treated with DG, the dose of gemcitabine administered was 93% of the intended dose. 21 patients are currently evaluable. 9 patients responded, including 3 CR and 6 PR. All responses were observed within the first 3 cycles.The ORR was 36% after DG (1 CR and 3 PR) and 50% after PDG (2 CR and 3 PR). Seven of 9 have progressed so far, with a median duration of response of 5 months (range: 3-11) and 2 received a consolidation treatment with rituximab (n=1) and cisplatin/etoposide (n=1) after 5 and 6 months while still on PR. With a median follow-up of 11.5 months (range:2.5-19.5), %17% patients are alive and 4 have died of disease progression(n=3) or multi organ failure (n=1). In patients treated with PDG, CTC grade 3-4 thrombopenia, anemia, neutropenia and infection were the main toxicities, recorded in 44%, 29% and 16% and 8% of cycles,respectively as compared to 9%,5% 4% and 4.5% in patients treated with DG. In conclusion, PDG is effective in heavily pretreated patients with MCL under the age of 70 but response duration is short and thrombocytopenia is the most significant toxicity. DG is also effective, even if to a lesser extent, and can be safely employed in elderly patients. A combination of both regimens with immunotherapy should be tested to improve ORR and response duration.

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DIALOG(R)File 5:Biosis Previews(R)

0014409346 BIOSIS NO.: 200300368065
Salvage Therapy with High Dose Cytarabine in the Treatment of Refractory or Recurrent Acute Leukemia.
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ABSTRACT: To study the curative effect of combination therapy based on high dose cytarabine in the treatment of refractory or recurrent acute leukemia, altogether 26 patients were included and observed. Therapy consisted of HD-Ara-C 2g/m2 every 12 hours on days 1 through 4; daunorubicin 45mg/m2/day, or mitoxantrone 10mg/m2/day, or VP16 150 mg/m2/day, or AMSA 100mg/m2/day on day 5 and 6. 13 patients achieved CR, 3 patients achieved PR. Among them 12 patients achieved CR after 1 course of therapy. The CR rate had nothing to do with patients' age; FAB type; white blood cell count; cytogenetics. After patients were followed up for 5apprx28 months, the 0.5 year DFS rate of CR+PR group vs NR group was 32.0% vs 14.3% (P<0.05). The 1 year OS rate was 21.9% vs 10.0%(P<0.05). No one died in the treatment period. The median time of white blood cell count below 1.0x109/L was %17% days (12-40 days). There was no neurotoxicity, nephrotoxicity or heart toxicity. Erythema or conjunctivitis was occurred in 1 patients. 3 patients had fever. Reversible hepatic disfunction was observed in 7 patients. Mucositis above 2 grade was occurred in 12 patients. Nausea, Vomiting and diarrhea above 2 grade was occurred in %17% patients. 21 patients had definitive infections, 2 of them had to postpone consolidation chemotherapy because of severe infection. G-CSF was used in 15 patients, which had no effect on patients' outcome. 10 of the 16 CR+PR patients relapsed within 6 months. 6 patients still were alive with disease free. Among them, high dose consolidation therapy was employed in 2 patients. 4 patients had undergone Allo-stem cell transplantations. Salvage therapy with HD-Ara-C was effective in the treatment of refractory or recurrent acute leukemia. Resembled report has not seen in China. The regimen was proved secure without severe complication. The side effect was relatively mild and reversible. But granurocyte recovery was quite long and accompanied by more chance of severe infection. G-CSF was always needed. Sometimes sterile laminar flow room was needed. HLA identical sibling or unrelated donor must be found soon after the patients obtained CR. Otherwise high dose consolidation therapy or auto-stem cell transplantation must be considered.

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DIALOG(R)File 5:Biosis Previews(R)

0014409330 BIOSIS NO.: 200300368049
Attenuated FLAIG Protocol for Elderly Patients with Acute Myeloid Leukemia.
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ABSTRACT: Introduction. The long-term prognosis of older patients with AML is dismal. The incidence of CR with standard chemotherapy is reduced and the remissions are usually transient, with less than 10% of the patients surviving beyond 3 years. Intensive treatments are burdened with an high incidence of treatment-related mortality. Palliative treatments do not reduce the time spent in the hospital nor transfusion requirements. We have therefore initiated a study with an attenuated FLAIG induction regimen, followed by outpatient consolidation and maintenance, to improve CR rates and try to reduce hospitalization. Patients and therapy. Forty-two elderly patients (median age 66; range 60-78) with AML "de novo" (AML=26 pts.) or secondary to an antecedent hematological disorder (sAML=16 pts.) were treated with Fludarabine 30 mg/m2/day in 30' followed 4 hours later by Cytarabine 1 g/m2/day in 3 hours (both for 5 days in pts. Itoreq70 or for 4 days in pts.>70). Idarubicin 10 mg/m2/day was administered as a 24-hours infusion on days 1,3,5. Glycosilated G-CSF was given from day 7 to granulocytes>1000. Patients in CR after induction were given two consolidation courses on an outpatient basis: the first with the same Fludarabine and Cytarabine scheme for two days plus Idarubicin on day 2 as a bolus infusion; the second with Thioguanine 50 mg/m2/day and Cytarabine 100 mg/m2/day subcutaneously for 5 days plus oral Idarubicin 15 mg/m2 on day 1. Maintenance with Thioguanine 50 mg/m2/day for 4 days plus Cytarabine 100 mg/m2 on day 5 every week was continued for at least one year or until relapse. Results. All patients are evaluable for response. CR was obtained in 27 pts. (64.3%). The incidence of CR was 69.2% in AML and 56.2% in sAML (p=.51). Eight pts. (19%) were resistant (5 AML and 3 sAML). Seven pts. (16.7%) died: 2 during induction (1 cerebral hemorrage, 1 ARDS) and 5 during the aplastic phase. The more relevant infectious complications were: 2 pulmonary aspergillosis (one causing patient's death while in CR) and other infections grade 3/4 according to WHO in 11 more pts. Moreover, in 2 pts. a prolonged post-remissional pancytopenia was observed, with positive CMV antigenemia, which resolved after antiviral therapy. The median length of hospitalization for the induction phase was 29.5 days (1-73). The consolidation phase required readmission in 15 pts. (55%) for a median of 20 days (14-69). The median overall survival (OS) was 7.4 months, with a minimum follow-up of 3 months for censored patients and with an actuarial probability of survival at 34 months of 19.8%. OS was significantly longer in patients Itoreq65 yrs than in those >65 yrs (22.3 vs. 4.1 months; p=0.01). The median disease-free survival (DFS) was 13 months and again it was longer in pts Itoreq65 yrs (%17%.5 vs. 6.8 months, p=0.04).Conclusion. This attenuated FLAIG protocol provided an high incidence of CR with acceptable toxicity in this high-risk group of patients. Better maintenance procedures should be devised to control the minimal residual disease and prolong the disease-free survival, possibly without further hospitalization to improve the quality of life and to contain the costs of treatment.

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DIALOG(R)File 5:Biosis Previews(R)

0014409328 BIOSIS NO.: 200300368047
Chemotherapy Priming with G-CSF in Acute Myeloid Leukemia (AML) Modifies Outcome. Report of a Prospective Randomized HOVON and SAKK Cooperative Group Study.
AUTHOR: Lowenberg Bob (Reprint); Vellenga Edo (Reprint); Gmur Jurg (Reprint); Theobald Matthias (Reprint); Dekker Adriaan W (Reprint); Fey Martin F (Reprint); De Greef Georgine E (Reprint); Schouten Harry C (Reprint); Ferrant Augustin (Reprint); Sonneveld Pieter (Reprint); Ossenkoppele Gerrit (Reprint); van Putten Wim L J (Reprint); Boogaerts Marc (Reprint)
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ABSTRACT: Exposure of myeloid leukemic cells to hematopoietic growth factors in culture results in metabolic and cell cycle activation which renders the leukemia more susceptible to killing by cytarabin. The concept of enhancing the efficacy of cell cycle dependent chemotherapy (CTX) by adding hematopoietic growth factors to the regimen has not been tested adequately in the clinical context mainly due to the use of antagonistic interfering chemotherapy or insufficient numbers of patients. We set out to test its validity in a randomized trial of newly diagnosed patients with AML (18-65 yrs; median 45) by adding G-CSF (lenograstim) consequently only during CTX of the first two induction cycles (Ara-C/idarubicin and Ara-C/amsacrin) but not on the days after chemotherapy during the aplastic phase. In order to allow for undisturbed synergy between Ara-C and G-CSF, Ida and Amsa were especially scheduled at the end of the cycle. Of 655 patients entered, 321 evaluable patients were allocated to the G-CSF treatment arm and 319 to the control induction (similar distribution of prognostic factors). In brief, overall outcome results (median follow-up for pts alive: 47 mo) compare as follows: the CR rate was slightly lower in the G-CSF arm 79.4 vs 83.1% (p=0.24), while disease free survival probabilities at 4 yrs were better in the G-CSF group (DFS 42 vs 34 %, p=0.04). There was a higher early death rate on induction treatment in the G-CSF group (%17%.2 vs 10.7%, p=0.02) which could not be pinpointed to a common cause. The higher early death rate in the G-CSF study arm was predominantly apparent among pts over 50 yr of age (24 vs 12%) and was not seen among patients below 35 yr (8 vs 7%). The increased early death rate was followed by a reduced relapse frequency and a reduced late mortality in the G-CSF treatment group which resulted in improved DFS. Other outcome estimates are: overall survival 40 vs 34%, event-free survival 33 vs %28%%. The DFS advantage associated with G-CSF treatment was restricted to pts of age < 50 yr and cytogenetically intermediate risk patients. These results indicate that the therapeutic synergy between Ara-C and G-CSF in AML can be exploited clinically when both agents are properly scheduled.

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DIALOG(R)File 5:Biosis Previews(R)

0014409021 BIOSIS NO.: 200300367740
A New Translocation, t(6,11), Involving the NUP98 Gene Translocation, in a Case of Secondary Myeloproliferative Disorder, Which Eventually Developed Clonal Evolution and Transformed to Acute Myeloid Leukemia.
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RECORD TYPE: Abstract
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ABSTRACT: NUP98 is one of frequent targets of chromosomal aberrations after chemotherapy and radiotherapy. Several chromosomal translocations have been reported between NUP98 at 11p15 and 1q23, 2q31, 5q35, 7p15, 8p11.2, 9p22, 11q22 or 20q11 in myeloid abnormalities. We discovered a new translocation, t(6;11)(p23;p15), with NUP98 gene in a patients with secondary myeloproliferative disorder, which eventually developed clonal evolution and transformed to acute myeloid leukemia (AML). A 59-year-old man presented leukocytopenia and generalized bleeding tendency in May 1998. A t(15;%17%)(q22;q21) translocation was identified by chromosome analysis, and the PML-RARalpha fusion gene was detected by fluorescence in situ hybridization (FISH) analysis. He was diagnosed as acute promyelocytic leukemia (APL). After achieving complete remission by ATRA treatment, he received consolidation chemotherapies including etoposide. He presented low grade fever and leukocytosis in March 2000. Bone marrow were hypercellular with mild dysplasia and 0.2% blast cells. Chromosome analysis by G-banding method showed t(6;11)(p23;p15) but no t(15;%17%). PML-RAR, MLL and BCR-ABL fusion genes were absent by RT-PCR. Additional karyotype abnormalities evolved increasingly. Five months later, leukocytosis with blasts with more complex karyotypic abnormalities, such as 48, XY, add(3)(p25), +8, der(11) t(6;11)(p23;p15), +21 or 48, XY, add(6)(q11), +8, der(11) t(6;11)(p23;p15), add(19)(q11), +21, appeared. The serum level of G-CSF and GM-CSF were within normal range. Uncontrollable skin involvement was observed. Chemotherapy including idarubicin and cytarabine temporarily eliminated the abnormal clone. Dual color FISH analysis was performed using some target gene probes and their internal control probes. Split signal of NUP98 was observed in 68.4% of 117 cells analyzed. However, the potential fusion partner of NUP98 gene such as HOX and DEC remained undetectable, and the fusion gene could neither be found by a differential display method. While the importance of the NUP98 N-terminal domain in leukemogenesis has been suggested by some investigators, the exact mechanism has not been well elucidated. On the other hand, 6p23, the abnormality of which is thought to be important in early tumorgenesis, is most often damaged after chemotherapy or radiotherapy. However, the molecular mechanism of 6p23 abnormality remains unclear. In the present study, we have shown that NUP98 gene is related to a novel translocation, t(6;11)(p23;p15), in a case of post chemotherapeutic myeloproliferative disorder followed by overt AML. Moreover, frequent chromosomal analysis showed that this abnormality placed at the start of clonal evolution to AML. This new chromosomal abnormality thus appears to be closely associated with the hematological malignancy. Further molecular studies are required to characterize the leukemogenesis associated with the translocation, and to identify the fusion gene and its product. The present data provide new information on further molecular characterization of NUP98 and 6p23 abnormalities in hematological malignancies.

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DIALOG(R)File 5:Biosis Previews(R)

0014408986 BIOSIS NO.: 200300367705
Effects of 5-aza-2'-deoxycytidine (DAC, decitabine) on Proliferation and Differentiation of Cytokine-Expanded Normal Human CD34+ Cells: A Model for Methylation Changes during Myeloid Maturation.
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JOURNAL: Blood 100 (11): pAbstract No. 4221 November 16, 2002 2002
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LANGUAGE: English

ABSTRACT: DNA methylation is a major epigenetic mechanism controlling tissue- and development-specific gene regulation. During normal hematopoietic cell maturation, methylation of myeloid-specific genes (e.g. myeloperoxidase (MPO), lysozyme (LZM), CSF receptors) is decreased concomitantly with differentiation (Blood 87:447-455,1996; Leukemia 13:530-534, 1999). Conversely, the S-phase-specific demethylating agents 5-azacytidine and 5-aza-2'-deoxycytidine (DAC) have shown a moderate differentiation-inducing activity on myeloid cell lines. To establish an

in vitro model of normal hematopoietic differentiation modulated by demethylation, we used CD34+ cells from apheresis specimens (AP) and analyzed proliferation, viability, CD15, LZM and MPO expression (FACS) with and without DAC treatment. Since DAC is ineffective on cells in G0, CD34+ cells from AP (being mostly in G0/G1) were cultured with serum containing medium (IMDM plus 10% FCS) (SCM, n=4) or serum-free medium (SFM, n=10) in the presence of Flt3, SCF, and IL-3 for 72 hours. Treatment with DAC was performed on day (d) 3 of culture, as three 24hr pulses with two low-cytotoxic concentrations (10, 50 nM). Cells were harvested on d7 of culture. Without DAC treatment, cell expansion under these conditions was 11.9 fold (range 0.36 - 22.8). With DAC pretreatment, growth inhibition was observed relatively to the expansion culture (median 13.9%, range -4.4 - 27.6% (10 nM DAC); median %17%.3%, range -13.9 - 47.7% (50 nM DAC)), as well as a slightly decreased cell viability (median 8.8%, range -5.8 - 46% (10 nM DAC); median %17%.7%, range -23.3 - 73.1% (50 nM DAC)). Interestingly, DAC induced an increase in LZM+ cells (median 14.1%, range 4.3 - 36.8% (10 nM DAC); median 19.8%, range 8 - 56.5% (50 nM DAC), n=7), and a lesser increase in MPO+ cells (median 0.4%, range -10.2 - %17%.5% (10 nM DAC); median 5.3%, range -9 - 19.5% (50 nM DAC)) and CD15+ cells (median 7.6%, range -10.8 - 22.4% (10 nM DAC); median 4.6%, range -24.7 - 33.8% (50 nM DAC)). In order to ask whether DAC pretreatment increases responsiveness of the cells to G-CSF, DAC treatment was followed by G-CSF (10 mg/ml) for 48 hours. Expectedly, G-CSF alone led to a substantial increase of LZM+ cells (median 36.7%, range 33 - 86.8%, n=5), MPO+ cells (median 21.1%, range 3.8 - 22.6%) and CD15+ cells (median 26.2%, range 14.8 - 44.1%). With DAC pretreatment, we detected an additive increase in LZM+ cells upon G-CSF-induced differentiation (median 49.1%, range 13 - 127.4% (10 nM DAC); median 50.8%, range 39.1 - 63.2% (50 nM DAC)), whereas no additional effect on expression of MPO (median 19.4%, range 4.6 - 50.5% (10 nM DAC); median 20.2%, range 6.8 - 29.8% (50 nM DAC)) or CD15 (median 23.7%, range -21.6 - 44% (10 nM DAC); median 33.2%, range 6.5 - 62.5% (50 nM DAC)) was noted. In conclusion, at low-cytotoxic concentrations DAC induces a dose-dependent inhibition of cell growth, and moderately increases differentiation markers in cytokine-expanded normal hematopoietic precursor cells. This effect was particularly evident for lysozyme expression. This model should be suitable for global analyses of multiple differentially methylated genes, to determine possible patterns of methylation and gene expression being established during lineage-specific maturation.

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DIALOG(R)File 5:Biosis Previews(R)

0014408960 BIOSIS NO.: 200300367679
Colony-Stimulating Factor (CSF) Treatment of Patients with Chemotherapy-Induced Febrile Neutropenia (FN): A Meta-Analysis of the Randomized Clinical Trials (RCTs).
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ABSTRACT: FN is a frequent and life-threatening event in cancer patients receiving chemotherapy. RCTs of CSFs along with empiric antibiotics in the treatment of established FN have demonstrated reduced duration of neutropenia but variable effects on duration of hospitalization and mortality. We report here a systematic review with a formal meta-analysis of CSFs for treatment of established FN. Medline, Embase and the Cochrane Controlled Clinical Trials Register were searched for RCTs comparing CSF and antibiotics vs antibiotics alone in the treatment of established FN. Of the more than 8000 references screened, 13 original reports including 1518 patients met eligibility criteria for the meta-analysis. Patients treated with CSF and antibiotics had shorter hospitalizations (OR=0.63; 95% CI, 0.49-0.82; P=.0006; 8 trials, n=1221) and a shorter time to neutrophil recovery (OR=0.32; 95% CI, 0.23-0.46; P<.00001; 5 trials, n=794). A reduction in infection-related mortality was also observed in association with CSF treatment (OR=0.51; 95% CI, 0.26-1.00; P=.05; 9 trials, n=872). A subgroup analysis of overall mortality and infection-related mortality demonstrated that patients with hematological malignancies did significantly better when treated with CSF (OR=0.32; 95% CI, 0.13-0.78; P=.01). Patients randomized to receive CSF experienced more bone pain, joint pain, or flu-like symptoms than controls (OR=2.05; 95% CI, 1.22-3.46; P=.007; 6 studies, n=622). Patients treated with G-CSF reported fewer symptoms than patients given GM-CSF (OR=6.27; 95% CI, 2.15-18.%28%; P=.0008). The CSFs can be combined with antibiotics in patients with established FN to improve outcomes including shorter hospital stays and may reduce the occurrence of infection-related mortality although the mortality reduction was sensitive to removal of one of the studies. Fewer side effects are reported with G-CSF compared to GM-CSF. The economic impact of CSF treatment of established FN is undergoing investigation.

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DIALOG(R)File 5:Biosis Previews(R)

0014408833 BIOSIS NO.: 200300367552
The Stress Associated Variant of Acetycholinesterase AChE-R Is Expressed during Human Hematopoietic Development and Its Cleavable C-Terminal Peptide ARP Stimulates Hematopoiesis.
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LANGUAGE: English

ABSTRACT: Hematopoietic stress responses involve increases in leukocyte and platelet counts, implying the existence of stress responsive factors that modulate hematopoiesis. Acetylcholinesterase (AChE) is expressed in mammalian neurons and hematopoietic cells. In the brain, it responds to stress by mRNA overexpression and alternative splicing, yielding the rare stress - associated "readthrough" AChE-R variant protein. This led us to explore the hematopoietic involvement of AChE-R and its unique C-terminal peptide ARP. To examine the relevance of AChE-R to human hematopoiesis its expression during early fetal development in the aorta-gonad-mesonephric region (AGM), liver, spleen, and bone marrow (BM) was studied by in situ hybridization. Changes in the expression of AChE variants were consistent with spatio-temporal shifts that occur during hematopoietic tissue development. Furthermore, the distal enhancer, proximal promoter and first intron of the human AChE gene revealed clusters of consensus binding sites for hematopoietically active and stress -induced transcription factors. Using high resolution in situ hybridization CD34+ cells from cord blood express the three known variant AChE-mRNAs, which displayed different intracellular distributions. AChE-R protein was found in 5-15% of adult peripheral blood, bone marrow and fetal CD34+ cells (both committed CD38+ and uncommitted CD38-) by flow cytometry. Dramatic increases were observed in the number of PB granulocytes and monocytes that express intracellular AChE-R following the stress of labor in post partum mothers, in cord blood or in PB following BM mobilization with

G-CSF compared to normal blood of non-stressed individuals. Externally supplied synthetic C terminal peptide ARP (2nM), by itself facilitated the proliferation of CD34+ cells in culture in an antisense suppressible manner. When combined with early acting cytokines, ARP enhanced the ex-vivo survival and expansion of CD34+ cells by 40-60 fold and significantly increased the number of early myeloid and megakaryocyte progenitors up to %28% days in culture. We present AChE-R, as a new stress marker in myeloid cells, and its C-terminal peptide ARP as a new growth modulator which may promote the myelopoiesis and thrombopoiesis characteristic of stress and may be utilized to enhance the efficiency of ex vivo expansion for bone marrow transplantation.

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DIALOG(R)File 5:Biosis Previews(R)

0014408810 BIOSIS NO.: 200300367529
Granulocyte Transfusions from G-CSF- and Dexamethasone-Stimulated Donors for Treatment of Patients with Severe Neutropenia-Related Infections.
AUTHOR: Lee Je-Jung (Reprint); Chung Ik-Joo (Reprint); Cho Sang-Hee (Reprint); Kook Hoon (Reprint); Hwang Tai-Ju (Reprint); Cho Duck (Reprint); Ryang Dong-Wook (Reprint); Kim Hyeoung-Joon (Reprint)
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LANGUAGE: English

ABSTRACT: Granulocyte transfusions have been used to treat severe, progressive infections in neutropenic patients who fail to respond to antimicrobial agents. Although corticosteroid or granulocyte colony-stimulating factor (G-CSF) were previously used separately to increase leukocyte counts in healthy donors, increasingly G-CSF and corticosteroids are used together, requiring the need to establish the efficacy of this mobilizing regime. This prospective study evaluated the safety and efficacy of granulocyte transfusion therapy from donors stimulated with a combination of G-CSF and dexamethasone, in 26 patients with severe neutropenia-related infections. To mobilize granulocytes, healthy volunteer donors received G-CSF, 5 mug/kg subcutaneously 12-14 hr before leukapheresis, and dexamethasone, 3 mg/m2 intravenously 15 min before leukapheresis. Donor neutrophil counts were 5,904+-764 muL-1 at baseline, 22,089+-818 muL-1 before the injection of dexamethasone, 23,891+-703 muL-1 immediately before leukapheresis, and 19,786+-802 muL-1 after leukapheresis. Eighty-nine leukapheresis procedures were performed with a mean yield of 8.8 X 1010 granulocytes (range: 0.2-%17%.9 X 1010). The mobilizing agents were well tolerated in the donors. Of the patients, 15 (57.7%) showed favorable responses, whereas 11 (42.3%) had unfavorable responses, including one patient in whom pulmonary edema worsened. Adverse reactions to the therapy were arrhythmia in two patients (7.6%) and pulmonary edema in one patient (3.8%). Favorable responses were seen in 81.8, 71.4, and 45.5% of the patients from whom fungal, Gram-negative, and Gram-positive organisms were isolated, respectively. This study suggests that the combination of G-CSF and dexamethasone is an effective, well-tolerated regimen for mobilizing granulocytes from healthy donors, and that granulocyte transfusion therapy is useful for neutropenic patients, especially those with fungal or Gram-negative infections that are resistant to appropriate antimicrobial agents.

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DIALOG(R)File 5:Biosis Previews(R)

0014408801 BIOSIS NO.: 200300367520
G-CSF Mobilized Granulocyte Transfusions in 20 Children with Neutropenic Sepsis.
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LANGUAGE: English

ABSTRACT: Introduction: Neutropenia is an important risk factor for infectious complications after chemotherapy and during stem cell transplantation (SCT). The results of G-CSF mobilized granulocyte transfusions (GTX) are heterogeneous, but especially in children promising. We report the results of a retrospective analysis of GTX in 20 children. Patients and methods: 20 children with hematological diseases, including ALL (-relapse), AML (-relapse), lymphoma and congenital immune deficiency syndromes. Age: 10 months to %17% years, bodyweight 8 kg to 68 kg. A SCT was performed in 11/20 children. GTX was initiated after failure of intravenous antibiotic or antimycotic therapy on an individual basis. GTX were harvested from healthy volunteers after stimulation with G-CSF (lenograstim, 5mg/kg bodyweight; 12 hours prior to apheresis) and dexamethasone (8mg p.o.). GTX were given in a 1 to 2 hours infusion on a twice or three times per week schedule after a premedication with clemastil and pethidine. Steroids were not routinely given. Results: In total, 112 GTX were given (1-13 per child, mean 5.6). The mean leukocyte count before GTX was 383/ml (25-850/ml), the mean leukocyte count one hour after GTX was 4351/ml (1200-18300/ml), the mean leukocyte count 24 hours after GTX was 2584/ml (475-9600/ml). The duration of neutropenia prior to the 1st GTX was 2 days to 60 days (mean 15 days). The total duration of neutropenia lasted from 6 days to 110 days, 2 children did not overcome neutropenia. 11/20 children died, 6/11 due to infections, 3/11 due to toxicity, 1/11 in respiratory failure, in 1 child the cause of death remained obscure. 3/7 children with a fungal infection died, 5/5 children with a viral infection died, 2/4 children with a bacterial infection died, 1/4 children with fever of unknown origin died.12/20 children suffered from additional complications (diffuse bleeding, pancreatitis, cardiac or renal insufficiency). Only 2/12 children with additional complications survived. 7/8 children without complication survived. 9/20 children needed artificial ventilation during GTX, 8 out of these children died. The duration of neutropenia before the 1st GTX (1-10 days vs. >10 days) did not influence the outcome, neither did the total duration of neutropenia (6-20 days vs. >20 days). Acute side effects (significant decrease in oxygen-saturation, hypotension, allergic reactions) requiring discontinuation of GTX occurred only very rarely. Conclusions: For overcoming neutropenia in children with refractory sepsis, GTX are efficacious and safe. The benefits in viral infections seem to be limited, but promising in fungal infections. In children requiring mechanical ventilation benefit from GTX was limited.

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DIALOG(R)File 5:Biosis Previews(R)

0014398999 BIOSIS NO.: 200300357718
Mylotarg (Gemtuzumab Ozogomycin: GO) Given Simultaneously with Intensive Induction and/or Consolidation Therapy for AML Is Feasible and May Improve the Response Rate.
AUTHOR: Kell Jonathan W; Burnett Alan K; Chopra Raj; Yin John; Culligan Dominic; Clark Richard; Hunter Ann; Rohatiner Ama; Milligan Don W;

Russell Nigel; Prentice Archie
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ABSTRACT: The feasibility of combining GO with intensive chemotherapy for induction and/or consolidation has been evaluated in 67 patients as a prelude to the MRC AML15 Trial. The aim was to combine Mylotarg (GO) with chemotherapy planned in the trial, (DAT; Daunorubicin, AraC, Thioguanine, or DA; Daunorubicin AraC; or FLAG-IDA; Fludarabine, AraC, G-CSF, Idarubicin) as course 1 which was given using GO 3mgs/m2 on day 1 of chemo in 55 patients (DAT= 33; DA= 8; FLAG-Ida= 14). Of 55 patients treated 41 (85%) entered CR with course 1 (DAT=26/32; DA=7/8; FLAG-Ida=8/8). Experience from MRC12 indicates that 64% of cases achieve CR with course 1. The median time to ANC recovery (1 x 109/l) was 27 days (range 19-54) and platelets > 100 x 109/l was 30 (range 21-48) which is within the mean + ISD of 720 patients treated with H-DAT alone on the MRC AML12 trial. Non-haemopoietic toxicity was confined to the liver. Overall the maximum toxicity was Grade 1 = 5pts, Grade 2 = 22pts, Grade 3 = 13pts and Grade 4 = 10pts. Of the Grade 3 and 4 toxicities 7 were felt to be definitely associated with Mylotarg therapy. A possible contributory factor was the inclusion of Thioguanine. Of the 39 recipients of Thioguanine schedules 22 developed Grade 3 or 4 liver toxicity compared with 1 for 16 recipients of non-Thioguanine schedules. Nine additional patients received H-DAT with 6mgs/m2 GO and 8 patients achieved CR with course 1. Haematological recovery was not prolonged, but 3 patients developed Grade 3 or 4 liver toxicity of whom 2 developed a VOD-like syndrome from both recovered. A 6mg dose was not considered feasible. 15 patients received GO 3mgs with courses 1 and 2 (DAT 3+10 and DAT 3+8). ANC recovery was delayed in 5 patients and platelet recovery in 11, and both in 5 patients. Grade 3 or 4 liver toxicity was seen in 3 cases of whom 2 developed a VOD-like syndrome. %17% patients have received GO 3mgs/m2 with chemotherapy course 3 (MACE: Amsacarine, AraC, Etoposide, or high dose AraC). Only one patient developed greater than Grade 2 liver toxicity. 12 patients have received induction course 1 with GO 3mgs and course 3 with GO 3mgs. This appears to be feasible but follow-up of this cohort is ongoing. The study was the pilot for the MRC15 trial which will compare DA +- GO (3mgs) vs FLAG-Ida +- GO (3mgs) as course 1 and MACE +- GO vs High dose AraC +- GO in consolidation. The overall survival of all patients receiving GO 3mgs with course 1 at 6 months is 73% and at 12 months 68% . For the patient receiving non-Thioguanine induction with 3mgs the 6 months survival is 91%.

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DIALOG(R)File 5:Biosis Previews(R)

0014398824 BIOSIS NO.: 200300357543
Treatment of Severe Multiple Sclerosis (MS) with High-Dose Immunosuppressive Therapy (HDIT) and Autologous Stem Cell Transplantation (SCT): 2 Year Follow-Up.
AUTHOR: Nash Richard A (Reprint); Bowen James D; McSweeney Peter A; Sullivan Keith M; Pavletic Z Steven; Maravilla Kenneth R; Al-Omaishi Jinan; Corboy John R; Derrington David; DiPersio John; Georges George E; Gooley Theodore; Holmberg Leona A; LeMaistre C Fred; Openshaw Harry; Ryan Kate; Sunderhaus Julie; Storek Jan; Zunt Joseph; Storb Rainer; Kraft George H
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective: To evaluate the stability of MS and safety of HDIT and autologous CD34-selected SCT with a median patient follow-up of 2 years. Methods: Autologous peripheral blood stem cells were mobilized with G-CSF (16 mug/kg/day) and CD34 selected using Isolex 300 (Nexell). HDIT consisted of TBI (800 cGy), cyclophosphamide (120 mg/kg) and ATGAM (90 mg/kg). Eligibility included an Extended Disability Status Scale (EDSS) score from 5.0-8.0 and an increase of one or more points in previous year. Twenty-one patients had failed previous therapy with interferon-beta and 15 had failed multiple therapies including copaxone, prednisone or methotrexate in addition to interferon. Results: Twenty-six patients (secondary progressive=%17%, primary progressive=8, relapsing-remitting=1), median age 41 (27-60) years were enrolled. Median EDSS at HDIT was 7.0 (5.0-8.0). Median follow-up was 29 (3-49) months. Early significant complications after HDIT were a MS flare during G-CSF for mobilization (n=1), EBV-posttransplant lymphoproliferative disorder (PTLD; n=1) and the engraftment syndrome (n=13). Late complications (>100 days) were infrequent. One patient developed a herpes simplex virus infection and 2 patients developed a varicella-zoster infection. All patients are now treated with antiviral therapy until 1 year after transplant. One patient developed hypothyroidism and another developed a Guillain-Barre syndrome and pneumonia at 12 and %17% months after HDIT and SCT, respectively. No secondary malignancies were observed. Of 25 evaluable patients, 6 have had an increase in the EDSS of gtoreq1.0 point (Kaplan-Meier (KM) estimate of progression at 2 years=27%). Four of these 6 patients progressed in the first year after HDIT. Three of 22 evaluable patients developed new or enhancing lesions on brain MRI after HDIT (including 1 related to G-CSF mobilization). Two deaths have occurred at day 53 from EBV-PTLD and at 23 months from bacterial pneumonia after continued progression of MS. The KM estimate of survival at 2 years was 91%. Conclusions: Late complications were infrequent after HDIT and SCT for severe MS. Although loss of neurological function continued in some patients, this was a heterogeneous group with advanced MS who had failed previous therapy. Treatment in earlier stages of MS possibly before the development of progressive disease may decrease the risk of continued loss of neurological function after HDIT. Controlled studies will be required to fully assess efficacy.

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DIALOG(R)File 5:Biosis Previews(R)

0014398800 BIOSIS NO.: 200300357519
Correction of Congenital Immunodeficiency Disease with Umbilical Cord Blood Transplantation.
AUTHOR: Kurtzberg Joanne (Reprint); Martin Paul L (Reprint); Driscoll Timothy (Reprint); Mustafa Mahmoud (Reprint); Wood Susan (Reprint); Kelly Tracy (Reprint); Szabolcs Paul (Reprint)
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LANGUAGE: English

ABSTRACT: Introduction: With the exception of X-linked, gamma SCID, the only curative therapy for children with congenital immunodeficiency syndromes (CID) is allogeneic stem cell transplantation. Many of these children lack a suitably matched related donor for the procedure.

T-depleted haplo-identical bone marrow transplantation from a parental donor has been used in some of the patients, but 50% never recover B-cell function with this approach. Unrelated bone marrow (BM) transplantation is associated with a high incidence of chronic graft-versus-host disease (cGvHD) and matched unrelated living donors are not available for many patients. Unrelated cord blood (UCB) is a readily available source of allogeneic stem cells that can be used without full HLA-matching. Thus, >95% of patients unable to identify a matched bone marrow donor can find a UCB donor matched at a minimum of 4/6 HLA loci. A significantly lower incidence of cGvHD (10%) has been reported with this donor source. We report our results using unrelated UCB transplantation (UCBT) as primary therapy for 22 pediatric patients with various CIDs. Methods: Twenty-two patients between 4 months and 4 years of age with a variety of CIDs (3 Severe Combined Immunodeficiency Disease; 4 Combined Immunodeficiency Disease, 1 Leukocyte Adhesion Deficiency, 4 Familial Erythrophagocytic Lymphohistiocytosis, 10 Wiscott Aldrich Syndrome) were prepared for transplant with busulfan 40mg/m2/dose PO q6Hx 16 doses/cyclophosphamide 50mg/kg/dose IV daily x 4 doses/Anti-Thymocyte Globulin 30mg/kg/dose IV daily x 3 and subsequently transplanted with UCB matching at 3 (n=1), 4 (n=11), 5 (n=7) or 6 (n=1) HLA loci. Cell doses were high with a median of 10.38 x 10e7 nucleated cells/kg (range 6.67-33.8) and 5.94 x 10e6 CD34 cells/kg (range 1.50-91.53) delivered by the graft. GvHD prophylaxis was administered with cyclosporine and intermedate dose methylprednisolone and supportive care provided with IVIG, G-CSF, low dose amphotericin-B, acyclovir, TPN, transfusions, low-dose heparin and emperic parenteral antibiotics for fever. Results: Engraftment occurred in all patients, including 1 patient who refused busulfan and required additional cyclophosphamide and a second graft. The median day to achive and ANC of 500/uL was 18 (range 7-45) and day to an untransfused platelet count of 50K/uL was 67 (range 31-189). Moderate to severe (grades II-IV) acute GvHD developed in 4/22 patients. Chronic GvHD developed in all patients with WAS (skin only in all but one patient who had extensive disease involving liver, gut and skin). Five patients died of infection (n=3), infection with EBVLPD and cGvHD (n=1) or VOD (n=1). The remaining %17% patients (77%) are fully engrafted with complete immune reconstitution of T and B cells with a median followup of 1605 days (range 182-2491). All patients were successfully immunized with live and killed vaccines after one year post transplant. Conclusion: We conclude that patients with various forms of CID can be successfully treated with UCBT early in the course of their disease. Full immune reconstitution combined with a low incidence of acute and chronic GvHD make this a preferred stem cell source for allogeneic transplantation for patients lacking matched sibling donors.

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DIALOG(R)File 5:Biosis Previews(R)

0014398776 BIOSIS NO.: 200300357495
Feasibility of Allogeneic Hematopoietic Stem Cell Transplantation with Reduced-Intensity Conditioning Regimens for Refractory Myeloid Malignancies.
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ABSTRACT: Purpose:To examine the feasibility and efficacy of reduced intensity hematopoietic stem cell transplantation (RIST) in elder patients(pts) with acute myeloblastic leukemia (AML) or myelodysplastic syndromes (MDS). Patients and Methods: Twenty-eight pts, who were ineligible for conventional allo-HSCT, underwent RIST from an HLA-matched, related donor between September 1999 and June 2002. The median age of the pts was 56 years (range, 45-67) and their diagnosis included AML (n=12), leukemia evolving from MDS (n=8), and MDS (REAB n=4, RA n=4). At the time of enrollment, 10 and 18 pts were categorized in the low- (acute leukemia or MDS RAEB in first CR, and MDS RA) and high-risk group (the others), respectively. RIST regimen was 1) cladribine 0.66 mg/kg for 6 days plus busulfan 8 mg/kg for 2 days with (n=7) or without rabbit ATG 2.5 mg/kg (n=1), or 2) fludarabine 180 mg/m2 for 6 days plus busulfan 8 mg/kg for 2 days with (n=1) or without ATG 2.5 mg/kg (n=19). All the pts received G-CSF-mobilized PBSC. Median number of CD34+ cells infused was 2.85 x 106//kg (range, 1.50-6.55 x 106/kg). GVHD prophylaxis consisted of cyclosporine alone (n=23) or cyclosporine plus short-term methotrexate (n=5). Regimen related toxicity (RRT) within %28% days was evaluated by the Bearman's criteria. Results: Except one patient with relapsed AML, 27 pts achieved engraftment, with a median of 13 days (4-18) to ANC >0.5 x 109 /L and 18 (10-34) days to platelets >20 x 109 /L. One developed grade III RRT within 30 days of transplantation (congestive heart failure, coma and respiratory distress), and three (11%) died without progression of primary diseases. Causes of deaths were bacterial infection (n=2), and acute GVHD (n=1). Fifteen developed acute GVHD (grade I, 5; grade II, 7; grade III, 2;grade IV, 1), and 12 developed chronic GVHD (limited, 3; extensive, 9). In the low-risk group, estimated 1-year overall survival (OS) and disease-free survival (DFS) were the same 86%. In the high-risk group, they were 85% and 59%, respectively. Seven of the 18 high-risk pts relapsed or progressed at a median of 205 days after transplantation (range, 0-728 days). Of these seven pts, five received ATG-containing preparative regimen and none subsequently developed grade II to IV acute GVHD. Of the nine high-risk pts who remained remission after RIST, one received ATG and six developed grade II to IV acute GVHD. Use of ATG and absence of > grade II acute GVHD were associated with relapse after RIST (p=0.0350 and 0.0114, respectively). Salvage therapies for relapse or progression following RIST included donor lymphocyte infusion (n=1), second RIST (n=3) and chemotherapy alone (n=3). Four pts who received DLI or second RIST achieved durable remission with a median duration of 365 days (range, 100-580 days). Conclusion: RIST can be performed safely in elder pts with myeloid malignancies, and exerts a therapeutic potential to those who failed conventional chemotherapy. There might be a possibility that altered immunological environment introduced by preceding RIST may make the recurrent leukemia more susceptible to salvage immunotherapy. Considering the significant association between GVHD or ATG and DFS, defined management of GVHD following RIST should become a major target of clinical research.

1/7/179
DIALOG(R)File 5:Biosis Previews(R)

0014398770 BIOSIS NO.: 200300357489
Lower Incidence of Bronchiolitis Obliterans (BO) in Allogeneic Hematopoietic Stem Cell Transplantation with Reduced-Intensity Conditioning Compared with Myeloablative Conditioning.
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ABSTRACT: Bronchiolitis obliterans (BO) is a late onset non-infectious pulmonary complication with significant mortality after hematopoietic stem cell transplantation (HSCT). Clinical manifestations of BO include symptoms such as cough, dyspnea and wheezing due to obstruction of small airways. Lung function tests and radiological findings are also indicative of airflow obstruction. The onset of BO varies from 80 days to as late as 2 years following HSCT. Chronic GVHD, methotrexate use and serum immunoglobulin deficiency had been pointed out to be risk factors for BO, but whether the intensity of conditioning regimen would affect the incidence of BO is unknown. We analyzed the incidence of BO in 144 consecutive patients who survived longer than 80 days after allogeneic HSCT. Median age was 40 years old (1-65); 87 patients were male and 57 were female. Ninety-five patients received grafts from a related donor and 49 from an unrelated volunteer donor. Fifteen of related donor had serologically one antigen mismatch in HLA. Ninety-six patients underwent HSCT with myeloablative conditioning (58 with cyclophosphamide/ total body irradiation, 33 with busulfan/ cyclophosphamide and 5 with others), while 48 patients with reduced-intensity conditioning (34 with fludarabine/ busulfan and 14 with cladribine/ busulfan). Stem cell sources were bone marrow in 52 patients and G-CSF mobilized peripheral blood stem cells in 92 patients. The diagnosis of BO was made based on clinical symptoms and either with decreased FEV1 for more than 50% from baseline or findings of chest radiographs and thin-section CT scans which suggest the existence of airflow obstruction. These findings include hyperinflation of lung field, wall thickening and dilatation of bronchi or bronchiole, decreased attenuation of vascular markings due to hypoxic vasoconstriction, and mosaic attenuation evident on end-expiratory, full-suspended maneuver. Cases with active infection that could cause airway obstruction were excluded. Fourteen patients (9.7%) developed BO at a median period of 221 days (102-350). Median age was 36 years old (4-53). Ten patients were female and 4 were male; there was a trend that female patients were more susceptible to BO (p=0.06). Thirteen patients received myeloablative conditioning, while only 1 received reduced-intensity conditioning. The cumulative incidence of BO at 2 years after HSCT was 2.3% with reduced-intensity conditioning compared to %17%% with myeloablative conditioning (p=0.03). Seven out of 14 cases with BO died; in 6 cases BO was the cause of death with or without infections. The incidence of BO in this analysis is higher than previous reports, which may be due to the fact that, by using radiological findings especially thin-section CT scan, we properly diagnosed the cases who might have been overlooked before. Multivariate analysis with selected variables (age, sex, conditioning regimen, donor -related or unrelated-, HLA mismatch, methotrexate use, chronic GVHD) confirmed that reduced-intensity conditioning was associated with lower incidence of BO. Chronic GVHD was not identified as a risk factor of BO in this analysis. These results indicate the importance of lung tissue damage by pre-transplant conditioning chemotherapy or irradiation in the pathogenesis of BO.

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DIALOG(R)File 5:Biosis Previews(R)

0014398733 BIOSIS NO.: 200300357452
Factors Influencing Collection and Outcome in Primary High-Risk and Relapsed Lymphoma: Prospective Analysis of Autologous Hematopoietic Stem Cell Transplantation (ASCT) in 202 Lymphoma Patients.
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ABSTRACT: ASCT following standard induction chemotherapy has repeatedly been reported beneficial for intermediate and high-risk as well as relapsed lymphoma (L), has shown impressive response rates in non-Hodgkin's (NHL), Hodgkin's lymphoma (HD) and multiple myeloma (MM) and is increasingly used in chemosensitive or refractory L pts. Here we report on 202 consecutive pts with newly diagnosed high-risk (n=87) or relapsed L (n=115) who received an ASCT between 1/97-6/2002. There were 132 males and 70 females, their median age at ASCT being 49 years (y, 21-70). 139 NHL (112 B-NHL, 19 T-NHL, 6 Burkitt), 24 HD and 41 MM pts were included, with 143 with intermediate or high IPI and 86 with bulky disease. Median chemotherapy cycles of 8 (1-20) were administered before ASCT. In 2/3 of the pts unselected PBSC (n=130) and in 72 pts with bone marrow involvement and/or stage IV disease selected cells were used. BM was employed in 2 pts with extensive pretreatment. The median number of collected and transfused CD34+ cells were 7 and 5x10e6/kg bw, respectively. High-dose (HD) chemotherapy consisted of BEAM in 146, busulfan-containing regimens (n=11), cyclophosphamide-containing regimens in 5 and HD-melphalan in 40 pts. The median WBC (>1000/muL) and platelet (>20.000/muL) engraftment was prompt on day 10 and 11, respectively. Median numbers of RBC- and Plt-transfusions of both 4 were given and hospital discharge was on day 16. With a median follow-up of 21 months (1-65) after ASCT, 136 pts (67%) are alive, with 80 pts remaining in CR, %17% in PR and 16 in SD (OR 56%). 66 pts have died, relapse being the most common cause of death. The transplant related mortality was 4%. Although both OS and OR were better in low-risk pts with 75% and 63% as compared to intermediate and high-risk pts with 57% and 53%, respectively, encouraging results were obtained in these generally high-risk pts, the most predictive value for long-term survival being response before ASCT. Comparing pts with retransfusion of <5 (group A), >5 (B) and >7x10e6/kg (C) CD34+ cells, these groups displayed similar pts characteristics, but showed prompter engraftment, fewer transfusions, lesser G-CSF administration and earlier hospital discharge in group B and C; the percentage of pts surviving was similar, but the OS duration was shorter with 26, 19 and 11 months, respectively. The comparison of <50y, >50y and >60y old pts displayed decreased CD34+ mobilization and shorter survival in older pts, but similar engraftment and other post-ASCT kinetics. Further subgroup analyses will be presented. Our result suggest that ASCT is beneficial for high-risk L pts, feasible without severe toxicity also in elderly and relapsed pts, and may improve OS and PFS. Pts well responding before ASCT are highly curable. Those with no response before ASCT have reduced OS and PFS rates and may benefit from novel strategies, including use of antibody-based therapies, in vivo purging, treatment of minimal residual disease post ASCT and/or use of non-myeloablative allogeneic transplantation.

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DIALOG(R)File 5:Biosis Previews(R)

0014398718 BIOSIS NO.: 200300357437
Ex-Vivo Culture-Expanded Parental Haploidentical Mesenchymal Stem Cells (MSC) To Promote Engraftment in Recipients of Unrelated Donor Umbilical Cord Blood (UCB): Results of a Phase I-II Clinical Trial.
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ABSTRACT: Suboptimal neutrophil engraftment after unrelated donor UCB transplantation (UCBT) may be due in part to changes in the microenvironment after intensive doses of chemoradiotherapy. In an attempt to speed neutrophil and platelet recovery, we co-infused ex vivo culture expanded parental haploidentical MSCs in pediatric patients undergoing unrelated donor UCBT for high risk acute leukemia. Bone marrow (35-112cc) was harvested from a haploidentical parental donor at time of referral. Cells were shipped to Osiris Therapeutics where MSCs were isolated and expanded. The goal was to infuse 5.0 x 106 MSC/kg recipient on day 0 and 21 after UCBT. Fifteen patients were enrolled. Seven were unevaluable either because UCBT has not occurred (n=2), death occurred before UCBT (n=1), UBCT occurred at other center (n=1), or because of insufficient MSC availability (n=3). Underlying diagnosis was ALL (n=6) or AML (n=2). Median age was 7.5 (0.2-16) years. Preparative therapy consisted of cyclophosphamide, TBI and ATG (n=7) or busulfan and melphalan (n=1). GVHD prophylaxis consisted of CSA and short course methylprednisolone. G-CSF 5 ugm/kg/day was given after transplant until neutrophil engraftment. UCB was HLA-A, B, DRB1 matched (n=1) or mismatched at 1 Ag (n=2), or 2 Ag (n=5). Median UCB cell doses were 3.1x107 nucleated cells/kg (2.0-12.4) and 5.9x105 CD34 dose/kg (3.1-34.8). Median MSC doses were 2.1x106/kg (0.9-5.0) on day 0. Only 2 patients received MSC on day 21 (1.0 and 0.06 x106/kg). Others did not due to insufficient growth. No serious adverse events occurred with MSC infusions. 8/8 evaluable patients achieved neutrophil engraftment (ANC >500/mm3) at a median of 19 days (range, 9-%28%). 6/8 evaluable patients achieved platelet >50,000/mm3 at a median of 1.7 months (range, 1.1-3.1). Three patients developed acute GVHD (1 grade I, 2 grade II). With a median follow-up of 1.7 years, 6 patients are alive and disease free. Two patients died from infections on days 53 and 63 days. In summary, infusion of ex vivo culture expanded haploidentical MSCs into UBCT recipients can be safely performed. Engraftment after UCBT may be enhanced with MSC infusions with prior experience suggesting a median time of engraftment of 23 days and 3 months for recipients of UCB in general. Due to logistical difficulties of obtaining haploidentical parental BM cells at time of referral, the use of universal MSC donor cells is currently being explored in a larger multicenter trial of unrelated donor UCB recipients.

1/7/182
DIALOG(R)File 5:Biosis Previews(R)

0014398707 BIOSIS NO.: 200300357426
Additional Transplantation of Ex-Vivo Generated Megakaryocytic Cells after High-Dose Chemotherapy: Results of a Pilot Study.
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ABSTRACT: The transplantation of ex-vivo generated hematopoietic (post)-progenitor cells in addition to a standard peripheral blood progenitor cell (PBPC) graft represents a promising approach to ameliorate high-dose chemotherapy (HD-CT)-induced cytopenia. Based on our previously reported preclinical results (Exp.Hematol. 2000, %28% :335-346), the current study aimed to investigate the feasibility of the large-scale expansion and additional transplantation of autologous megakaryocytic cells. PBPC for the ex-vivo expansion were collected in addition to an unmanipulated graft following standard-dose chemotherapy plus G-CSF-mobilization, and CD34-cells were selected by MACS (purity 84% - 99%, n = 4). CD34pos-PBPC (0.5 x 106 /kg, n = 1; 1.0 x 106 /kg, n = 3) were cultured in serum-free medium stimulated with SCF (10 ng/ml), IL-3 (10 ng/ml) and TPO (100 ng/ml) for 7 days (7-day culture, 7d, n = 3) and 12 days (12d, n = 1). Total nucleated cells were expanded 3.1 - 9.5-fold (7d) and 14.6-fold (12d), corresponding to 80.0 - 710. x 106 TNC/kg and 1,460 x 106 TNC/kg, respectively. CD34pos-cells were expanded 1.5- to 5.5-fold (7d) and 0.7-fold (12d). The fractions of CD61pos expanded cells were 7.0 - 18.9% (7d) and 0,7% (12d). CD41pos-cells were 10.3 - 25.8% (d7) and 2.6% (12d). Three patients (metastatic breast cancer, n = 1; testicular cancer, n = 2) received 7-day expanded cells and 1 patient (metastatic sarcoma) received 12-day expanded cells 24 hours after non-myeloablative HD-CT and PBPCT (3.0 - 4.8 x 106CD34pos -PBPC/kg). The ex-vivo generated cells were well tolerated and no adverse effects were recorded. Fast hematopoietic recovery (absolute neutrophil count, ANC; platelets, PLT) was observed in every one patient (days to ANC > 100/mul: 8 - 10; days to ANC > 500/mul: 9 - 10; days to PLT > 20,000: 10 - 12). Plt counts < 20,000/mul were observed on 2 - 7 days and a median of 1 (range 1- 3) allogeneic platelet transfusion was necessary. Interestingly, one patient who received unmanipulated plus ex-vivo generated cells after the second of two high-dose chemotherapy courses (tandem PBPCT) required only one PLT transfusion after the second course whereas three PLT concentrates had to be administered after the first HD-CT course (PBPCT without ex-vivo generated cells). Taken together, the data demonstrated that the additional transplantation of ex-vivo generated megakaryocytic cells was safe and did not induce any side effects. However, the additional transplantation of ex-vivo generated cells was not related to a clear beneficial effect on hematopoietic recovery.

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DIALOG(R)File 5:Biosis Previews(R)

0014398691 BIOSIS NO.: 200300357410
Use of Total Leukocyte and Platelet Counts To Guide Stem Cell Apheresis in Healthy Allogeneic Donors Receiving G-CSF.
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ABSTRACT: Blood is increasingly being used as the source of hematopoietic stem cells for allogeneic transplantation. Healthy donors are usually mobilized with G-CSF, and leukapheresis is started on day 4 of G-CSF administration. While the first day's stem cell collection is sufficient in most donors, it is poor in some who do better the next day. Some donors require an increase in the G-CSF dose to beyond the usual 10 mug/kg. A pre-apheresis peripheral blood CD34+ cell count of gtoreq20/muL is predictive of a adequate collection. We studied 75 apheresis procedures on 35 normal donors collected from July 2001 to August 2002 to identify factors correlating with the peripheral blood CD34+ cell count which could be used to guide collections. Cobe Spectra cell separators running the MNC protocol (Version 6.1) were used. Donors were healthy

siblings (%17%-60 years, median 48) treated with apprx10 mug/kg G-CSF rounded off to the nearest vial size. The data shown represent each individual procedure. The median (range) hemoglobin, and leukocyte and platelet counts were 13.5 (9.8-16.7), 35.4 (18.1-68.3) x 109/L, and 144 (49-374) x 109/L, respectively. The median peripheral blood CD34+ cell count was 35/muL (range 3-187). The median (range) total number of CD34+ cells collected (106) and the collection efficiency were 230 (range 33-1501), and 52% (range 3-214), respectively. Linear regression showed a strong positive correlation between the peripheral blood CD34+ cell count and the total number of CD34+ cells collected (r=0.82; P<0.0001). There was a positive correlation between the total leukocyte and the peripheral blood CD34+ cell counts (r=0.32; P=0.006). There was a positive correlation between the platelet and the peripheral blood CD34+ cell counts (r=0.45; P<0.0001). Hemoglobin, hematocrit, albumin, or creatinine did not correlate with the number of CD34+ cells in the peripheral blood or the number collected. In multivariable analysis, the platelet and leukocyte counts were found to be significant independent predictors for good peripheral blood CD34+ cell counts. The combination of leukocytes gtoreq25 and platelets gtoreq100 was associated with good mobilization, good collection, and a high probability of harvesting an adequate number of CD34+ cells with a single apheresis. This is not the case with autologous donors (patients) in whom there is no correlation between the leukocyte or platelet counts and the number of CD34+ cells in the peripheral blood because of varying extent of prior therapy and different techniques of mobilization (e.g. chemotherapy). Based on these data, we suggest harvesting normal donors without necessarily checking and awaiting a peripheral blood CD34+ cell count result if the leukocytes are gtoreq25 and the platelets are gtoreq100. For those who do not satisfy both criteria, it is prudent to check the peripheral blood CD34+ cell count and subject them to apheresis only if the mobilization is adequate with a peripheral blood CD34+ cell count of gtoreq20.

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DIALOG(R)File 5:Biosis Previews(R)

0014398690 BIOSIS NO.: 200300357409
Single Blinded, Randomized Study of Low-Dose Cyclophosphamide Followed by G-CSF or Sequential GM-CSF/G-CSF for Mobilization of CD34+ Cells To Support Autologous Transplantation- Interim Analysis.
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ABSTRACT: G-CSF and GM-CSF are both approved for mobilization of CD34+ cells for autologous BMT, in conjunction with chemotherapy. Most studies have shown that larger doses of mobilization chemotherapy result in higher CD34+ cell counts. However, lower doses are likely to be associated with fewer side effects. It is also not known if sequential GMCSF/GCSF is as effective as GCSF. In a prospective, study, we compared the results of large volume leukapheresis in 35 patients with hematologic malignancies who had received cyclophosphamide 1.5 g/m2 followed by G-CSF 10mcg/kg/d (days 2-15) (n = %17%) or GM-CSF 250ug/m2 (days 2-8) followed by G-CSF 10mcg/kg/d (days 9-15) (n=18). Investigators were blinded to group assignment. Circulating CD34+ cell counts were monitored, and large volume leukapheresis (12-30L) (Cobe spectra, Gambro LCT, Lakewood CO) was started when predicted CD34+ collection for 18 L volume exceeded 4 million /kg or higher. Flow cytometry was used for cell enumeration. Adverse events during mobilization were limited to recurrence of chronic atrial fibrillation in one patient. There were no episodes of neutropenic fever, or platelet transfusions during this phase. The results of leukapheresis are presented below: Cell counts in the apheresis product showed a trend towards higher values in the sequential group, compared to the GCSF group, for NK cells (p = 0.07) but not T cells (p = 0.11) or CD 34+ cells (p = 0.81) (t test, unequal variances). To date, 29 patients have undergone high dose chemotherapy and autologous transplant, with the following results: In this study, GCSF and a sequential combination of GM-CSF and G-CSF both resulted in collection of adequate CD34+ cells after low-dose cyclophosphamide. The low dose of cyclophosphamide resulted in few adverse events. The trend towards higher NK cell numbers in the apheresis product after use of the sequential regimen warrants further study, since these cells are known to have important immunological functions.

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DIALOG(R)File 5:Biosis Previews(R)

0014398684 BIOSIS NO.: 200300357403
Mobilization of Peripheral Blood Stem Cells (PBSC) from Healthy Donors: Daily Single Versus Divided Doses of G-CSF (filgrastim).
AUTHOR: Hamaki Tamae; Iijima Kimiko; Komeno Yukiko; Yuji Koichiro; Mitani Kinuko; Kojima Rie; Imataki Osamu; Yoshihara Satoshi; Kim Sung-Won; Kusumi Eiji; Ando Toshihiko; Hirai Hisamaru; Aoyagi Arina; Kami Masahiro; Miyakoshi Shigesaburou; Ohashi Kazuteru; Kanda Yoshinobu; Arai Yukihiro; Tanosaki Ryuji; Ueyama Jun-ichi; Mori Shin-ichiro; Japan Hematology and Oncology Clinical Study Group
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ABSTRACT: Backgrounds: It is unclear whether filgrastim (recombinant granulocyte colony-stimulating factor: G-CSF) mobilizes more PBSC when administered in divided doses or in a single dose. In this prospective randomized, open labeled, multicenter study, we compared these two methods of G-CSF administration for the mobilization of CD34+ cells. Patients and Methods: Between April 2001 and May 2002, 71 consecutive donors (%17% to 65 years of age) who underwent PBSC harvest for allogeneic transplantation were randomly assigned to receive either a single subcutaneous injection of G-CSF at a dose of 400 mug/m2 x 1 / day for 3 days (Group A) or double subcutaneous injections at a dose of 200mug/m2 x 2 / day for 3 days (Group B). Both groups were comparable with regard to sex and age. Leukapheresis for PBSC collection was started on the 4th day. . In this analysis, only the cell yield obtained by the first apheresis was compared. To make the two groups similar, G-CSF was skipped on day 4 in both groups, and was resumed after the first apheresis as necessary to achieve the targeted CD34+ cell dose. The secondary endpoint was the difference in events associated with PBSC harvest; total nucleated cells collected, adverse events, pain assessment, and hospitalization. Statistical analysis was performed using Fisher's exact test, Wilcoxon's rank-sum test and the two-tailed paired t-test. Results: A total of 71 aphereses were performed. In all of the donors, G-CSF injection and apheresis were well tolerated. When the apheresis products obtained on the first day were analyzed, there was no significant difference in the total yield of CD34+ cells between groups A (1.7 x 106 cells per kg body weight of the donors(/ kg); 0.21 - 12.4 x 10 6 /kg) and B (2.3 x 106 /kg; 0.49 - 14.73 x 106 /kg: p=0.3571). There was also no difference in the total number of nucleated cells between groups A (6.4 x 108 / kg; 2.49 - 12.85 x 108 /kg) and B (6.3 x 108 /kg; 2.839 - 14.825 x 108 /kg: p=0.6288). Adverse events including mild to moderate bone pain and thrombocytopenia were transient and well

tolerated. In addition, there were no significant differences in the frequency or severity of toxicity or pain as assessed by the Visual Analogue Scale between the two groups. Conclusions: The present results suggest that there were no significant differences in the protocols for mobilizing PBSC using G-CSF administered in daily single vs divided doses.

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DIALOG(R)File 5:Biosis Previews(R)

0014398683 BIOSIS NO.: 200300357402
Fludarabine Plus Cyclophosphamide as Front Line Therapy in Chronic Lymphocytic Leukemia (CLL) Durably Impairs Steady State G-CSF Peripheral Blood Progenitor Cells (PBPC) Mobilization and Harvest.
AUTHOR: Tournilhac O (Reprint); Cazin B (Reprint); Lepretre S (Reprint); Divine M (Reprint); Maloum K (Reprint); Delmer A (Reprint); Grosbois B (Reprint); Feugier P (Reprint); Maloisel F (Reprint); Manhes G (Reprint); Villard F (Reprint); Villemagne B (Reprint); Bastit D (Reprint); Belhadj K (Reprint); Azar N (Reprint); Guibon O (Reprint); Travade P (Reprint)
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ABSTRACT: High dose therapy with autologous PBPC transplantation is increasingly used in CLL patients. Conflicting data have been published concerning the possibility to harvest PBPC after Fludarabine (FDR) containing regimens. We report our experience of steady state PBPC mobilization and apheresis in 38 CLL patients (from 9 centers) in complete remission (n=26), partial remission (n=11) or non evaluable (n=1) after FDR plus Cyclophosphamide (Cy) therapy. All these previously untreated stage B (n=34) or C (n=4) patients (median age : 53.9 years, range 38-66) had been enrolled in a trial assessing the impact of 6 courses (every 4 weeks) of oral FDR (30 mg/m2/d day 1 to 5) plus oral Cy (200 mg/m2/d day 1 to 5). Following FDR-Cy treatment, these 38 patients underwent a total of 52 steady state PBPC mobilizations (1, 2 or 3 mobilizations, in 25, 12 and 1 patients respectively) using either G-CSF (10 mug daily per kilo) or rHuG-CSF (7 mug daily per kilo) administered SC for 4 to 6 days. Apheresis were performed when circulating CD34 cells reached 0.01x10E9/L in order to collect at least 2x10E6 CD34 per kg of body weight. For the 52 mobilizations, median time (T) between the day 1 of the last FDR-Cy course and the day 1 of mobilization was 203 days (range 69 to 573). Following their first mobilization, only 30% of patients reached the level of 0.01x10E9/L circulating CD34 cells. This level was not significantly correlated to T, initial stage, remission status, hemoglobin, neutrophils, lymphocytes counts prior to mobilization but was strongly correlated to platelet counts evaluated 2 months after the last course of FDR-Cy (p=0.0099) or immediately prior to mobilization (p=0.008). In %17% patients (45%) no apheresis were performed because of mobilization failure. In the 21 remaining patients (55%) the median number of CD34 collected was 2.25x10E6 per kg of body weight (range 0.47 to 4.9). The goal of 2x10E6 CD34 per kg was obtained for only 13 patients (34%) after 1 (n=3 patients), 2 (n=9) or 3 (n=1) mobilizations and 2 (n=3 patients), 3 (n=2), 4 (n=6) or 5 (n=2) apheresis. Hence, we assume that prior treatment with FDR-Cy, even given as front line therapy, can considerably and durably impair further steady state PBPC harvest in order to rescue myeloablative regimens.

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DIALOG(R)File 5:Biosis Previews(R)

0014398680 BIOSIS NO.: 200300357399
Treatment Modalities and Success Rate of 1,907 Procedures of Peripheral Blood Progenitor Cell Mobilization: A Multicenter Study from GITMO (Gruppo Italiano Trapianto Midollo Osseo).
AUTHOR: Tarella Corrado (Reprint); Pompei Federica (Reprint); Cavazzuti Lorenzo (Reprint); Bacigalupo Andrea (Reprint); Arcese Wiliam G (Reprint)
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ABSTRACT: PBPC mobilization and collection is widely employed in autotransplantation. The success of the procedure depends on several factors, including mobilizing treatment and status of the underlying disease. In order to further investigate these aspects, data were collected from 1,907 mobilization procedures performed by 49 Centers associated to the GITMO during the year 1999. Patients (pts.) had a median age of 47 yrs., the F/M ratio was 922/985 and the diagnosis was: acute myeloblastic leukemia (AML) for 226 pts. (11.8%), acute lymphoblastic leukemia for 76 pts. (4%), non-Hodgkin's lymphoma for 572 pts. (30%), Hodgkin's Lymphoma for 44 pts. (7.6%), multiple myeloma for 385 pts. (20.2%), solid tumor for 424 pts. (22.2%), non-malignant disease for 80 pts. (4.2%). The mobilizing treatment was part of the front-line induction therapy in 1,336 pts. (70.4%), whereas 560 pts. (29.3%) underwent mobilization for refractory or relapsed disease. Mobilization was induced by G-CSF + chemotherapy at high-dose (hd) in 1,078 pts. (56.5%) or at conventional dose in 609 pts. (31.9%), or by G-CSF alone in 206 pts. (10.8%) (other procedures: 14 pts., 0.7%). When combined with chemotherapy, G-CSF was employed at 5 mcgr/kg/day in 1,277 pts. (76%) or at higher doses in 405 pts. (24%). Patients displaying signs of mobilization underwent PBPC collection. According to the total collected CD34+ve cells x10e6/kg b.w., two main groups were considered, i.e.: a. Poor Mobilizers (PM), collecting <2x10e6 CD34+ve cells /kg (366 pts., 19.2%) and b. Good Mobilizers (GM), collecting gtoreq2x10e6 CD34+ve cells /kg (1,541 pts., 80.8%). We identified the following factors predictive of reduced mobilization: i. mobilization schedule (25% PM with G-CSF alone vs. 18% with chemotherapy + G-CSF); ii. disease type (34% PM in AML at induction vs. 11% PM in all other diseases); iii. disease status at mobilization (%28%% PM in refractory/relapsed disease vs. 15% PM in first line); iv. peripheral blood counts at the mobilizing treatment (%28%% and 23% PM if WBC were <4000 and Platelets were <150.000, respectively, vs. 16% PM with higher blood counts). On the contrary, PBPC mobilization was not significantly influenced by: i. dose of chemotherapy (high or conventional); ii. dose of G-CSF (5 mcgr/kg/day or higher); iii. disease other than AML; iv. bone marrow involvement. In conclusion, the study indicates that: i. AML at diagnosis and refractory/relapsed malignancy are conditions associated with increased risk of poor mobilization; ii. a small though not negligible group of patients may display poor mobilization even if the procedure is performed as first line treatment; iii. for poor mobilizer patients, the use of high-dose chemotherapy or high dose G-CSF does not seem to offer greater chances of good mobilization and alternative approaches including new cytokines or combination of cytokines should be considered. The study was supported by a grant from DOMPE' BIOTEC S.p.A - Italy

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DIALOG(R)File 5:Biosis Previews(R)

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Spleen Size Transiently Increases in G-CSF-Mobilized Peripheral Blood Stem Cell Donors.
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ABSTRACT: Peripheral blood stem cell (PBSC) donors may experience splenic enlargement after 5 days of granulocyte colony-stimulating factor (G-CSF) administration and, more rarely, splenic rupture. Donors with the greatest increase in spleen size may be at the greatest risk of rupture. We studied the incidence and time course of splenic enlargement in allogeneic PBSC donors. Twenty healthy adults were given G-CSF 10 mug/kg/d for 5 days and a PBSC concentrate was collected by apheresis 2 to 18 hours after the last dose. Craniocaudal spleen length was assessed by ultrasound prior to G-CSF, immediately post-apheresis, and 3 to 4 days post-apheresis. Median donor age was 34 years (range 21 to 55). Twelve donors were male, 13 Caucasian, 4 African American, 2 Hispanic and 1 Asian. The effects of donor age, gender, race, and changes in blood counts, CD34+ cell counts, and blood chemistries on spleen length change were analyzed. Spleen length increased in 19 of 20 donors, and was significantly greater on the day of apheresis than at baseline ($p < 0.002$). The mean increase in length was 1.6 +- 1.3 cm or %17%.1 +- 16.8%. Spleen length increased 20% or more in 7 subjects; 5 were male and 5 were Caucasian. Three to 4 days post-apheresis, spleen length fell below levels on the day of apheresis ($p < 0.001$), but remained slightly greater than baseline ($p = 0.04$). There was no difference in percent spleen length change from pre-G-CSF to the day of apheresis among males versus females ($p = 0.39$) or among Caucasians versus non-Caucasians ($p = 0.50$). There was no relationship between subject age and change in spleen length or percent change in length ($r = -0.006$ and $r = 0.03$). Pre-G-CSF blood counts and chemistries were not related to changes in spleen length, but alkaline phosphatase and total bilirubin levels on the day of apheresis were related to changes in length ($r = 0.483$, $p = 0.03$ and $r = 0.481$, $p = 0.03$, respectively) and percent change in spleen length ($r = 0.51$, $p = 0.02$ and $r = 0.56$, $p = 0.01$). Neutrophil counts were related to spleen length only when both neutrophil counts and length were expressed as percent change from baseline levels. Greater increases in apheresis day neutrophil counts were associated with greater increases in spleen length ($r = 0.52$, $p = 0.024$). In conclusion, a 5-day course of G-CSF causes splenic enlargement in nearly all PBSC donors. The enlargement is quickly reversible, but is marked in some donors and may increase the risk of splenic rupture. Greater alkaline phosphatase and bilrubin levels on the day of apheresis were associated with greater increases in spleen size. Further studies are needed to identify factors which predict a greater risk of splenic enlargement and hence, of spontaneous rupture of the spleen.

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DIALOG(R)File 5:Biosis Previews(R)

0014398593 BIOSIS NO.: 200300357312
Hematological Recovery after Administration of Subcutaneous Alemtuzumab (MabCampath(R)) in Previously Untreated Versus Refractory B-CLL.
AUTHOR: Lundin Jeanette (Reprint); Kimby Eva (Reprint); Mellstedt Hakan (Reprint); Dyer Martin J S (Reprint); Hillman Peter (Reprint); Kennedy Ben (Reprint); Osterborg Anders (Reprint)
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ABSTRACT: The humanized monoclonal antibody alemtuzumab (MabCampath(R)) targets the CD52 antigen, which is expressed on normal B- and T-cells as well as on leukemic B-CLL cells. Alemtuzumab given iv achieved a clinical response in 33% patients with fludarabine-refractory CLL (Keating MJ et al, Blood 2002;99:3554-61). Here, we compare parameters for hematological recovery after sc alemtuzumab treatment in 43 previously untreated patients and 13 heavily pretreated refractory B-CLL patients. Untreated patients received alemtuzumab sc 18 weeks as previously described (Lundin J et al, Blood 2002;100:768-73); refractory patients received alemtuzumab sc 12 weeks. Response rates to primary therapy (n =43) were 78% (%17%% CR) and 62% (31% CR) following salvage therapy (n =12). Following alemtuzumab, fewer previously untreated patients develop cytopenias, but in all cases these were reversible and achieved normal levels within 1 month post-treatment (see table), with 14% patients receiving G-CSF support (four untreated and two refractory patients). Anemia was rare, only two patients in each group experiencing grade 3 as worst grade on-study. Transfusion support was more extensive in refractory patients. By end of therapy (EOT), improvements were seen in many patients with severe cytopenias at baseline; of refractory patients, four had baseline grade 3 to 4 thrombocytopenia (EOT, two had improved to grade 1 and 2) and one had grade 4 neutropenia (EOT, grade 1); of untreated patients, two had baseline grade 3 neutropenia (EOT, grade 1 or 2), one had grade 3 thrombocytopenia (EOT grade 2), and two had grade 3 anemia (EOT, grade 0 and 1). At EOT, all cases of anemia were grade 2 or below. These results demonstrate that hematological side-effects following alemtuzumab are manageable and reversible, with the majority of nadirs being short-lived. Hematological recovery was exceptionally prompt in previously untreated patients.

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DIALOG(R)File 5:Biosis Previews(R)

0014398545 BIOSIS NO.: 200300357264
Final Analysis of a Randomized Study on the Value of Fludarabine in Addition to ARA-C and G-CSF in the Treatment of Patients with High Risk Myelodysplastic Syndromes and Elderly AML.
AUTHOR: Ossenkoppele Gerrit (Reprint); Graveland W (Reprint); Sonneveld P (Reprint); Daenen S (Reprint); Biesma D (Reprint); Verdonck L (Reprint); Schaafsma M (Reprint); Westveer P (Reprint); Peters G (Reprint); Noordhuis P (Reprint); Muus P (Reprint); Selleslag D (Reprint); Holt B van der (Reprint); Delforge M (Reprint); Lowenberg B (Reprint); Verhoef G (Reprint); BIOSIS (Reprint)
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ABSTRACT: Fludarabine in addition to Arabinosylcytosine (ARA-C) increases the accumulation of ARA-CTP, an active metabolite responsible for the cytotoxic effect in leukemic blasts. Based on a variety of clinical studies, chemotherapy consisting of Fludarabine, ARA-C and G-CSF designated as FLAG has been suggested to provide effective antileukemic therapy and thus FLAG is now commonly employed for treating patients with MDS and AML. However the value of FLAG has never been critically assessed in appropriate comparative studies. A total of 134 pts with high risk MDS or AML above 60 years were randomized to receive induction therapy

consisting of ARA-C (2 g/m2 days 1-5) with or without Fludarabine (25 mg/m2 days1-5) (cycle I). Patients in CR or PR received an identical second cycle of chemotherapy (cycle II). Patients in CR or in PR after cycle II in both arms were consolidated with Daunorubicin (45 mg/m2 days 1-3) and ARA-C (200 mg/m2 days 1-7). Patients in both arms received G-CSF during and after chemotherapy of all cycles. 91 patients were diagnosed high risk MDS, their median age was 64 years (range 24-75), while 43 patients had AML (median 67 years; range 61-75). Overall, the CR rate with ARA-C/G-CSF was 65% versus 71% with FLAG (p=0.49). In AML FLAG treatment resulted in a significantly better CR rate (95% vs 71%, p=0.026). 32 patients (24%) are still alive with a median follow up of %28% months (range 14-59). Overall survival (OS) at 24 months was for the ARA-C/G-CSF arm 24% and 39% for the FLAG arm (p=0.32). Two years event free survival (EFS) was 10% and 19% (p=0.54) respectively. Fludarabine did not delay the median time to granulocyte (0.5x109/l) and platelet (20x109/l) recovery (19 and 20/21 days in both groups) after the first cycle. However recovery times after the second cycle were longer in the FLAG arm (granulocytes: 22 vs 18 days, platelets: %28% vs 21days). Septicemia (grade III-IV) was observed more often in the FLAG treated patients (55% vs 38% in the ARA-C/G-CSF arm, p=0.06). Grade 3-4 neurotoxicity was greater in the Fludarabine group(14% vs 3%, p=0.06). Multivariate analysis revealed prognostic factors for several end points:High bilirubin has adverse prognostic value for OS and EFS, low platelet count and cytogenetics for CR, OS and EFS while higher age has a bad prognosis for CR and EFS. MDS at last was an adverse factor for CR and EFS. In a selected cohort of patients we studied the in vivo accumulation of ARA-CTP in the leukemic cells. ARA-CTP accumulation at the end of the ARA-C infusion varied between 6.1 and 87.5 pmol/106 cells (mean 38.7+- %28%.2; n=6) while in the 6 FLAG treated patients the ARA-CTP accumulation was significantly (p=0.004) higher and varied between 107.9 and 337.3 (mean 183 +- 99.1). These results do not provide support for the postulated clinical effectiveness of FLAG as compared to single agent ARA-C. Although ARA-CTP accumulation in leukemic cells after FLAG is enhanced, clinical outcome in terms of CR rate, OS, EFS and DFS is not significantly improved by addition of Fludarabine to ARA-C.

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DIALOG(R)File 5:Biosis Previews(R)

0014398525 BIOSIS NO.: 200300357244
Significance of Myelosuppression (MS) during the Course of Therapy with Imatinib in Patients with Chronic Myelogenous Leukemia (CML) in Chronic Phase.
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ABSTRACT: Imatinib induces high rates of hematologic and cytogenetic response in patients (pts) with CML. Toxicity is minimal but some pts develop significant MS during the course of therapy. Grade gtoreq3 neutropenia and thrombocytopenia is reported in 35% and 20% of pts respectively. Treatment interruption and/or dose adjustments are frequent for these levels of MS. The significance of MS (and the associated dose interruptions) are not known. We investigated the frequency and significance of MS among 143 patients with late chronic phase CML treated with Imatinib at a starting dose of 400 mg daily after failing interferon (IFN) therapy. Grade gtoreq3 MS during treatment, represented by thrombocytopenia (platelets <50 x109/L) and neutropenia (absolute neutrophil count <109/L), was investigated as a prognostic factor for achieving major or complete cytogenetic (CG) remission. Time to MS (first episode during first 3 months of treatment versus at a later time) or MS lasting for >2 consecutive weeks was related to achievment of major CG remission. This duration of MS frequently has led to the recommendation to hold therapy and decrease the dose of Imatinib; although none of these pts received a daily dose of <300mg. The median age was 56 years (range, 24 to 81 years), median time from diagnosis 31 months (range, 5 to 221 months), median starting WBC 9.3 x109/L (range 1.8 to 135.9 x109/L) and platelets 278 x109/L (range, 92 to 1117 x109/L). The distribution by response to IFN was: 24 (%17%%) pts hematologic failure, 70 (49%) cytogenetic failure, and 49 (34%) intolerant. The median follow-up is 29 months (range, 6 to 31 months). A major CG remission was obtained in 99 pts (69%)\{77 (54%) complete, and 22 (15%) partial\}. Baseline prognostic factors associated with major CG remission were similar to those previously reported for a larger group of patients: initial WBC count (p = .01), platelet count (p = .0003), presence of peripheral blood blasts (p = .002), basophilia (p = .01), and percent Ph+ chromosome positivity (p = .01). The rate of major and complete CG remission by MS group was as follows:We conclude that the occurrence of Grade gtoreq3 MS, particularly when lasting for >2 weeks during Imatinib therapy for CML, is associated with a low probability of response to Imatinib. Since MS for >2 weeks was linked to dose interruption/reduction, it cannot be established whether this is direct reflection of the MS or a dose/response effect. Use of G-CSF for neutropenia and IL-11 for thrombocytopenia, rather than dose interruptions/reductions, may improve the results.

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DIALOG(R)File 5:Biosis Previews(R)

0014398498 BIOSIS NO.: 200300357217
HIGH-Dose CHOP and Midcycle Methotrexate for Adult Burkitt and Burkitt-Like Lymphomas.
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ABSTRACT: Burkitt (BL) and Burkitt-like (BLL) lymphomas are categorized as high-grade, biologically aggressive B-cell malignancies. Patients diagnosed with BL or BLL typically present with disease related symptoms, advanced stage, rapidly growing tumors, and extranodal involvement. There is no standard treatment for adult BL and BLL. Published series of adult patients typically report complete response (CR) rates of 80-100% and 2-year event free survival (EFS) ranging from 60-90%. The Magrath regimen has the best-reported results in adults, but the median age in their series was only 24 years. This is a complex regimen, utilizing 2 intrathecal agents, 7 different intravenous cytotoxic agents, plus leucovorin and mesna. Patients are receiving some form of intravenous therapy for 12/15 days during the CODOX-M portion. Based on the SWOG four-arm trial for large cell lymphomas, which showed CHOP to be as effective as more complex regimens, we hypothesized that a simpler regimen may be as effective for BL and BLL. From January of 1995 to August of 2002 at the University of Wisconsin Hospital and Clinics, 11 patients with Burkitt or Burkitt-like lymphoma were treated with a multidrug regimen consisting of HIGH-dose CHOP, midcycle methotrexate, and monthly intrathecal methotrexate. The treatment regimen is as

follows: cyclophosphamide 2 gm/m2 IV on days 1 and 2 (total dose 4 gm/m2), doxorubicin 25 mg/m2/day IV on days 1 and 2 (total dose 50 mg/m2), vincristine 2 mg IV on day 1, prednisone 100 mg PO on days 1-5, and 12.0 mg IT methotrexate, followed by midcycle methotrexate 3 gm/m2 IV on day 15. Supportive care included vigorous IV hydration, G-CSF support after each cycle, prophylactic TMP-sulfa, acyclovir, and fluconazole, and leucovorin rescue after IV methotrexate. Mesna was not given routinely during the high dose cyclophosphamide. Cycles were repeated every %28% days for a total of 4 cycles. Patient characteristics were as follows: median age 51 (33-71), BL 10 patients, BLL 1 patient, 7 patients stage IV, 1 patient stage IIIE, 1 patient stage III, 1 patient stage IIE, and 1 patient stage IE. No patients had HIV infection. Results: 10/11 patients achieved CRs (91%). One patient progressed while on therapy. The EFS is 73% and the overall survival (OS) is 82% at a median follow up of 22 months. Two patients recurred after the achievement of CR. One died from complications of allogeneic bone marrow transplantation, and the other has relapsed after autologous stem cell transplantation. Treatment-related toxicities included severe myelosuppression in nearly all patients, associated neutropenic fevers/infections, and tumor lysis syndrome requiring hemodialysis in 2 patients. There has been no hemorrhagic cystitis. There have been no treatment-related deaths. Conclusion: HIGH-dose CHOP with midcycle methotrexate produces response rates which appear comparable to more complex regimens and has an acceptable toxicity profile. Additional patients and longer follow-up are needed to better assess the efficacy of this regimen in regards to EFS and OS.

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DIALOG(R)File 5:Biosis Previews(R)

0014398407 BIOSIS NO.: 200300357126
Optimising Culture Conditions for the Growth of ALL Progenitor Cells.
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ABSTRACT: Only a minority of acute lymphoblastic leukaemia (ALL) cells are thought to be capable of proliferating to maintain the leukaemic clone. These cells may be the most relevant to characterise and subsequently target with treatment regimens. Several reports have investigated the growth of ALL blasts in short-term assays. However, ALL cells with colony forming ability are low in number and it is likely that they are not representative of the clonogenic population, which maintains the disease. Here, we have attempted to evaluate and optimise the culture conditions which support the long-term growth of leukaemic cells. Proliferation of ALL cells was evaluated in serum free suspension culture (SC) supplemented with a number of cytokines or in long term bone marrow stromal culture (LTBMC) with and without cytokine stimulation. Cultures were maintained for up to six weeks with weekly half-media changes. Cell counts, viability and karyotypic analyses were performed at regular intervals throughout the culture period. ALL cells from 37 patients (pts) at diagnosis (8 pre B, 1 pre pre B, 1 pre T-ALL, 5 T-ALL, 18 c-ALL, 3 bilineage) and 1 c-ALL in relapse, were grown in SC supplemented with Flt3, IL-3, IL-6, GM-CSF, G-CSF and SCF (F36GMGS). Cells were maintained for at least 4 weeks in %28% pts and to 6 weeks in 22 of these pts. Cell numbers were expanded (2-42 fold) from 5x105 up to 2.1x107 cells in 20 pts. FISH analysis was possible on 10 of the 20 pts cells that proliferated in the SC system. In 5 cases the cultured ALL cells had the same karyotype as was seen at diagnosis. In the remaining 5 cases, where cells with an abnormal karyotype could not be detected, proliferation was observed up to week 6 in only 2 of these cases. Cells from the 10 pts with a normal karyotype were evaluated by routine morphological analyses. In 8 of these cases, the majority of the cells present were undifferentiated blasts (range 59-85%). Proliferation of ALL cells from every subtype was observed in the SC system, interestingly expansion of cells was seen in all 8 pre-B samples. A number of cytokine combinations were evaluated in the SC system for their ability to support growth of ALL cells. The combinations F36GMGS, which supports growth of primitive normal and AML cells, or IL-3, IL-7 and SCF, which is thought to stimulate common lymphocyte progenitor cells, were the most effective in maintaining and expanding ALL cells in this system (from 5x105 at initiation to Itoreq7.1x106 and Itoreq9x106 cells respectively, P>0.1). The growth of ALL cells from 10 pts was compared in SC and LTBMC+- IL-3, IL-7 and SCF. The majority of cells had died by day 14 in LTBMC without cytokines and by day 21 in LTBMC with cytokines, while same pts cells could be maintained and expanded up to 6 fold, from 5x105 up to 2.9x106 cells in SC for up to 6 weeks. Removal of sera from the LTBMC system had no effect on proliferation of ALL cells. The number of cells proliferating in SC was up to 56 fold higher than that observed in the standard LTBMC (19x105 vs. 0.3x105, PItoreq0.03). Likewise, up to 48 fold more cells were present in SC than in serum free LTBMC (19x105 vs. 0.4x105, PItoreq0.02). In summary, we have developed a serum free SC system, which supports the growth of ALL cells for up to 6 weeks in the majority of our pts. Growth of ALL cells was superior in this SC assay than in long term bone marrow stromal cultures +- cytokines.

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DIALOG(R)File 5:Biosis Previews(R)

0014398274 BIOSIS NO.: 200300356993
All-Trans Retinoic Acid (ATRA) Endows G-CSF Responsiveness to NB4 Cells Via Upregulation of the G-CSF Receptor.
AUTHOR: Enriquez Louie (Reprint); Maun Noel (Reprint); Khanna-Gupta Arati (Reprint); Zibello Theresa (Reprint); Gaines Peter (Reprint); Berliner Nancy (Reprint)
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ABSTRACT: Several lines of investigation suggest that G-CSF can augment all-trans retinoic acid (ATRA)-induced neutrophil differentiation in acute promyelocytic leukemia (APL). Using EPRO cells overexpressing the G-CSF receptor (EPRO-GR), we showed previously that ATRA and G-CSF appear to regulate neutrophil differentiation by divergent pathways (Blood Vol 98, Supp. 1, p290a,2001). ATRA-mediated differentiation of EPRO-GR cells occurs via a retinoic acid response element (RARE)-dependent, STAT-independent pathway, while G-CSF-mediated differentiation occurs via a RARE-independent, STAT-dependent pathway. Here we examined G-CSF-mediated and ATRA-mediated differentiation in the APL cell line, NB4. As reported by others, we observed that G-CSF in the absence of ATRA is incapable of inducing NB4 cell maturation. However, ATRA induction of NB4 cells results in marked upregulation of G-CSFR mRNA and protein. G-CSFR does not appear to be a direct target of ATRA, since transcriptional upregulation does not occur in the presence of cycloheximide. ATRA-mediated differentiation of NB4 cells is associated with upregulation of G-CSFR, but not phosphorylation of STAT3 (Tyr 705), a critical signaling event during G-CSFR-mediated differentiation. ATRA-induced NB4 cells subsequently exposed to G-CSF show STAT3

phosphorylation, suggesting that ATRA enables the acquisition of G-CSF responsiveness. We then further characterized the effects of G-CSF alone on NB4 cells rendered G-CSF responsive by 24 hour exposure to ATRA (ATRA'apprx>G-CSF). NB4 cells primed with ATRA and then placed into growth medium were used as a control (ATRA'apprx>Uninduced). Morphologic differentiation is seen in both ATRA'apprx>G-CSF and ATRA'apprx>Uninduced cells. Cell cycle analysis by flow cytometry for incorporation of propidium iodide (PI) showed that ATRA-mediated differentiation is associated with a marked decrease in the percentage of cells in the S-phase (15.05%) and the G2/M-phase (3.22%) when compared to uninduced cells (S-phase: 54.3%; G2/M-phase: 9.04%). This decreased proliferation is associated with morphologic maturation. In contrast, G-CSF exposure does not alter the cellular proliferation of NB4 cells (S-phase: 56%; G2/M-phase: 5.79%) when compared with uninduced cells. ATRA'apprx>G-CSF (G0/G1-phase: 69.69%) and ATRA'apprx>Uninduced (G0/G1-phase: 76.82%) cells both revealed cell cycle arrest. To assess the correlation of G-CSF surface expression with total mRNA and protein levels we used flow cytometry for biotinylated G-CSF binding. In this analysis, G-CSFR was upregulated in both ATRA'apprx>G-CSF and ATRA'apprx>Uninduced cells. Because ATRA-induced differentiation proceeds autonomously in NB4 cells after only a short exposure to ATRA, we were unable to distinguish an independent role for G-CSF in the induction of maturation in this model. However, the observation that the initial expose to ATRA makes NB4 cells capable of G-CSF-dependent STAT signaling leads us to hypothesize that ATRA-induced upregulation of G-CSFR may induce G-CSF responsiveness in primary APL cells. We speculate that it may explain the reported response of t(11;%17%) APL (which is ATRA-resistant) to the combination of ATRA and G-CSF. Further characterization of the molecular events underlying these distinct pathways may further elucidate the mechanism of G-CSF augmentation of ATRA effects and may lead to novel therapeutic approaches to APL.

1/7/195
DIALOG(R)File 5:Biosis Previews(R)

0014397974 BIOSIS NO.: 200300356693
Short Intensified Therapy and Autologous Stem Cell Transplantation in Adult Burkitt Lymphoma. Excellent Results without High-Dose MTX.
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ABSTRACT: For adult patients with Burkitt lymphoma most treatment schedules incorporate high-dose intravenous methotrexate (MTX). We conducted a multicenter phase II study (HOVON-27) to investigate the efficacy of two short high-dose induction chemotherapy courses without high-dose MTX, followed by BEAM and autologous stem cell transplantation (ASCT) in poor risk NHL. Interim results of %28% patients with Burkitt lymphoma are presented. Inclusion criteria: Burkitt lymphoma, no prior treatment; age < 66 yr; Ann Arbor stage II-IV, or stage I bulky (> 10 cm) or LDH > 1.5 N; WHO performance score 0-2; no CNS localization; bone marrow involvement < 30% (histology); no leukemic phase. Treatment: Induction-1: cyclophosphamide 2 g/m2 day 1,2; doxorubicin 35 mg/m2 day 1,2; prednisone 100 mg day 1-5. Induction-2: mitoxantrone 30 mg/m2 day 1; etoposide 500 mg/m2 day 1-4; prednisone 100 mg day 1-5. G-CSF was given in both cycles from day 5 until recovery. Autologous stem cells were harvested after cycle 1 or 2 in the absence of bone marrow involvement. Patients with at least PR after cycle 2 went on with BEAM and ASCT. Consecutive cycles were given as soon as possible after hematological recovery. Intrathecal MTX 15 mg was given as CNS prophylaxis. After ASCT, radiotherapy to initially bulky PR-sites was allowed. Results: As of August 2002, data from %28% patients were available. Age median 35 years (range %17%-64); stage III/IV: 43%; bulky: 43%; bone marrow involvement 4%; E-sites > 1: 21%; LDH > N: 64%. Treatment on protocol was completed by 25(89%). Radiotherapy was given to 5 (%17%%). No toxic deaths were observed. Response on protocol was CR 24 (86%), PR 2 (7%). At a median follow-up of 36 months of patients still alive, 6 patients have died (all due to NHL). The actuarial 3 year survival estimates are: OS 76%, PFS 70%, EFS 69%. Conclusion: This short front-line high-dose sequential chemotherapy plus ASCT, without high-dose MTX, is highly effective in adult patients with Burkitt lymphoma.

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DIALOG(R)File 5:Biosis Previews(R)

0014397720 BIOSIS NO.: 200300356439
Topotecan, Cytosine Arabinoside and G-CSF (TAG) Versus Idarubicin, Cytosine Arabinoside and G-CSF (IDAG) in Patients with Myelodysplastic Syndrome (MDS) or MDS in Transformation: A Randomised Phase III Study.
AUTHOR: Guilhot Francois (Reprint); Bouabdallah Reda (Reprint); Desablens Bernard (Reprint); Guerci Agnes (Reprint); Ferrant Augustin (Reprint); Chopra Rajesh (Reprint); Amrein Philip (Reprint); Saba Hussain (Reprint); Dharan Bernie (Reprint); Gress Michael (Reprint); Camlett Ina (Reprint); Ross Graham (Reprint)
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RECORD TYPE: Abstract
LANGUAGE: English
ABSTRACT: Outcomes following therapy for MDS remain disappointing, despite the recognition of several new drugs which have activity against the disease. Recent publications (Beran et al 2000) have shown that topotecan, an inhibitor of topoisomerase I, is active in this disease. A Phase III study was conducted between Nov 1998 and Sept 2001 to compare two active regimens in patients (pts) with MDS, high risk RAEB, RAEB-t or poor risk AML from a preceding phase of MDS. Pts with relevant pathology and performance status (PS) 2 or better with no previous therapy (except low dose ara-C, hydroxyurea, or intrathecal methotrexate or ara-C) were included. Candidates for potentially curative allogeneic bone marrow transplantation were excluded. Pts were randomised to either TAG (T: Topotecan 1.25 mg/m2/day continuous infusion for 5 days; A:Ara-C 1 g/m2 IV over 2 hours daily for 5 days; G:G-CSF, 5 mg/kg/day sc injection from day 14 until neutrophil recovery); or IDAG (ID: Idarubicin12 mg/m2/day by slow IV injection daily for 3 days; A: Ara-C 1 g/m2 IV over 2 hours daily for 5 days; G: G-CSF, 5 mg/kg/day sc injection from day 14 until neutrophil recovery). Courses were repeated every 4-6 weeks until best response was achieved. Pts whose disease entered complete response (CR),partial response (PR) or haematologic improvement (HI) were to receive 2 consolidation courses. A total of 238 pts were enrolled. Age, sex and subgroups of MDS or AML were equally distributed in each arm. Proportion of pts older than 65 was similar: 47.9% and 40.3% for the TAG and IDAG groups respectively. As of September 2001a documented response (CR, PR, HI) was seen in 66 (55.5%) pts treated with TAG (95% CI: 46.5%, 64.4%) and 72 (60.5%) pts treated with IDAG (95% CI: 51.7%, 69.3%). Overall median survival for the two treatment regimes was similar: 44.3 weeks for TAG and 43.7 weeks for IDAG. Kaplan-Meier analysis revealed similar survival distributions between the 2 treatment groups (Log-rank

p=0.27). Grade 3/4 anemia, neutropenia and thrombocytopenia were recorded in 79% and 66%, 96% and 90%, 100% and 100% of pts for the TAG and IDAG regimes respectively. Most frequently grade 3/4 non-hematologic toxicities such as fever, sepsis and respiratory disorder were recorded in 31% and 35%, 26% and %28%%, 5% and 18% of pts for the TAG and IDAG regimes respectively. Serious adverse events were observed in 67 pts (56%) with TAG and in 72 pts (61%) with IDAG. Major reasons for cessation of treatment were completed treatment and adverse events for 85 (71%) and 68 (57%) pts, and for 22 (19%) and 34 (29%) pts for the TAG and IDAG regimes respectively. Overall, 90 pts (76%) died with TAG and 80 pts (67%) with IDAG. Major causes of death were hematologic toxicity and progressive disease for 6 (5%) and 3 (3%) pts, and for 65 (55%) and 46 (39%) pts for the TAG and IDAG regimes respectively. In conclusion, this study did not demonstrate differences between the groups with respect to response rate and overall survival.

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DIALOG(R)File 5:Biosis Previews(R)

0014397696 BIOSIS NO.: 200300356415
Oral vs Intravenous Consolidation Chemotherapy in Elderly Patients with AML. Results of the EORTC-GIMEMA AML-13 Phase III Trial.
AUTHOR: Jehn Ulrich (Reprint); Suciu S (Reprint); Thomas X (Reprint); Varet B (Reprint); Muus P (Reprint); Berneman Z (Reprint); Marie J P (Reprint); Broccia G (Reprint); Fillet G (Reprint); Mandelli F (Reprint); Nobile F (Reprint); Ricciuti F (Reprint); Leone G (Reprint); Willemze R (Reprint); Rizzoli V (Reprint); Montanaro M (Reprint); Denzlinger C (Reprint); Leoni P (Reprint); Beeldens F (Reprint); Vignetti M (Reprint); Amadori S (Reprint)
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ABSTRACT: A total of 757 pts (age 61-80 years, median 67 yrs) with either de novo (n=589) or sAML (n=168) were accrued between 12/1995-10/2001. For induction, they received 1 or 2 cycles of MICE (mitoxantrone 7mg/m2/day on days 1, 3 and 5 as 30 min. i.v. infusion; etoposide 100 mg/m2 days 1, 2, 3 as 1 hr infusion, and Ara C 100 mg/m2 on days 1-7 as continuous i.v. infusion). In a first step they have been randomized to either G-CSF 150 ug/m2 by 30 min. i.v. days 1-7, or days 8-%28%, or days 1-%28%, or none. CR-rate was 51%, PR 3%, refractory disease 25%, early death 2.5%, hypoplastic death 10.8%. Pts in CR were randomized in a 2nd step for 2 cycles of consolidation consisting of either i.v. mini-ICE (idarubicin 8 mg/m2/day on days 1,3 and 5 as i.v. infusion; etoposide 100 mg/m2 days 1, 2, 3 as 1 hr i.v. infusion; Ara C 100 mg/m2 days 1-5 as contin. infusion) or oral mini-ICE (idarubicin 20 mg/m2/day on days 1, 3, 5; etoposide 100 mg/m2, two times daily days 1, 2, 3; Ara C 50 mg/m2 days 1-5 twice daily s.c.). The aim of the study was to detect a difference in median DFS (time from 2nd randomization until relapse or death) from 7 to 10 months between the ORAL (experimental arm) and IV arm (control arm). A total of 346 pts were randomized for this question. At the time of analysis, the median follow-up was 2.67 yrs; a total of 224 relapses and 29 deaths in CR have been reported, and a total of 218 pts died. Type of induction treatment, age, disease, WBC, number of induction courses to reach CR and cytogenetic subgroups were well balanced in both groups. A total of 322 (93%) pts received the first consolidation. Among them, 52 pts had stem cells mobilized for autoSCT. 177 (51%) pts received the 2nd consolidation. The maximum toxicity during consolidation 1 and 2 was similar in both arms. However, the rate of grade 3-4 nausea was 9% vs 4% in the ORAL vs IV arm, grade 3-4 vomiting was 11% vs 2%, and grade 3-4 infection was 20% vs 27%. The time to platelet recovery > 20 x 109/L and > 150 x 109/L was significantly faster in pts receiving oral mini-ICE, both following course 1 and 2. The difference regarding PMN recovery > 0.5 x 109/L or 1.5 x 109/L was not statistically significant. The duration of hospitalization was significantly shorter during the first consolidation in the ORAL vs IV arm. The difference between the two arms, ORAL vs IV, regarding DFS was not statistically significant: p=0.22, hazard ratio = 1.%17%, 95% CI (0.91, 1.50), median = 0.75 vs 0.89 yrs. Similarly, regarding the duration of survival: p=0.33, hazard ratio = 1.14, 95% CI (0.88, 1.49), median = 1.31 vs 1.48 yrs. In conclusion, the ORAL consolidation arm was associated with more nausea and vomiting, shorter duration of recovery and less grade 3-4 infection as compared to the IV arm. Given the 253 events (relapses or death in CR) reported, the difference in terms of DFS was not statistically significant.

1/7/198
DIALOG(R)File 5:Biosis Previews(R)

0014397680 BIOSIS NO.: 200300356399
Significant Dose Escalation of the CHOEP Regimen in Young Patients with Aggressive Non Hodgkin's Lymphoma Is Feasible: Results of a Prospective Randomized Phase I/II Trial.
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LANGUAGE: English

ABSTRACT: We have previously shown that CHOEP (CHOP+etoposide) improves treatment results in young patients with aggressive NHL. The aim of this trial was to show the feasibility of dose escalation of CHOEP. To evaluate the maximum dose of CHOEP in either 14- or 21-day intervals, a phase I/II multicenter prospective randomized dose finding trial (High-CHOEP(HC)) was started that evaluated 4 dose levels of an escalated CHOEP-regimen supported by G-CSF in pts with newly diagnosed aggressive NHL aged 18-60 years. Doses per each of 6 planned cycles were as follows (dose levels DL 1-4): Cyclophosphamide, 1000/1200/1400/1600 mg/m2, doxorubicin 55/60/65/70 mg/m2, etoposide 375/450/525/600 mg/m2, vincristine 2 mg, prednisone 500 mg. Close monitoring of each cycle as well as rapid dose reductions in the case of toxic events was performed in order to define the dose level for each new patient entering the study. Recruitment was stopped when a stable DL was reached. Dose limiting toxicity (DLT) was defined as thrombocytopenia <80.000 on d 14 and leucopenia 4 days) neutropenia and thrombocytopenia <20.000/mul in HC21. Results: Between 2/98 and 6/00, 139 pts (HC14: 47, HC21:92, imbalance due to earlier reached DLT in 14-day regimen) were registered, all 119 eligible pts are evaluable, median observation time of 32 months. Pt characteristics: 88.7% B-NHL, median age 45 (20-60) years, male/female 74/45 pts, IPI 0/1 52.9% (36.6% in HC14, 61.6% in HC21), IPI 3 / 4 47.1% (63.4% in HC14, 38.4% in HC21), LDH elevated 69.7%, bulky disease 61.3%. Median treatment duration was 87 days in HC14 and 108 days in HC21. In HC14, DLT was reached at DL 2, in HC21 at DL 4. Platelet/packed cell transfusions / interventional antibiotics were necessary in >50% of cycles. CR-rate was 67.5% in HC14 and 80.8% in HC21. %28% pts have died (25 due to lymphoma, 1 TRM, 1 secondary AML, 1 other disease). 2-yr-SV is 71.4% (95%-CI 57-85%) in HC14 and 80.4 % (72-90%) in HC21. 2-yr TTF rates are 57.2% (42-73%) for HC14 and 71.8% (62-82%) for HC21. Conclusion: Significant dose escalations of CHOEP are possible with G-CSF support;

doses reached are higher in HC21 than in HC14 due to longer time needed for hematopoietic recovery. To determine whether etoposide dose escalation translates into higher efficacy, HC21 at DL 3 was chosen as the test arm of a phase III trial comparing standard CHOEP-21 with escalated CHOEP-21 in young pts with IPI 0/1 aggressive NHL that has already accrued >200 pts.

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DIALOG(R)File 5:Biosis Previews(R)

0014397669 BIOSIS NO.: 200300356388
Randomized Comparison of G-CSF Versus GM-CSF + High Dose Chemotherapy for Peripheral Blood Stem Cell Mobilization and Autologous Transplantation in Multiple Myeloma.
AUTHOR: Arora Mukta (Reprint); Burns Linda J (Reprint); Barker Juliet N (Reprint); Miller Jeffrey F (Reprint); Olujohungbe Adebayo B (Reprint); Weisdorf Daniel J (Reprint)
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Multiple myeloma is a malignant proliferation of plasma cells which despite multi-agent combination chemotherapy, is not curable with conventional therapy. Autologous PBSCT appears to offer higher response rates and improved survival rates. However this requires effective cytoreduction and rapid hematologic reconstitution to allow moderation of transplant associated morbidity and mortality. We conducted a randomized clinical trial to assess the efficacy of combination chemotherapy + G-CSF versus GM-CSF for PBSC mobilization and engraftment followed by autologous transplantation. The percentage of patients achieving CR to total therapy determined at day +%28%, +100 or 6 months post transplant and overall and disease free survival were major end points of the study. Eligible patient received Cyclophospamide (4gm/m2), Mitoxantrone (8gm/m2 QD x 2 days) and Dexamethasone (20mg/m2 Q 12 hours x 2 days) followed by randomization to either GM-CSF or G-CSF daily until completion of third or final leukapharesis. For each of the 2 cycles of chemo priming patients were followed daily with outpatient visits till completion of leukapharesis. Cytoreductive preparation for transplant was with Cyclophosphamide (75mg/kg QD x 2 days) + TBI (165 cGy BID x 3 days). Maintainance immunotherapy with alpha interferon was used post transplant. We report interim results on 54 patients. 68% of patients had stage III disease at diagnosis, 54% underwent more than 4 cycles of initial chemotherapy and 13% had only minimal response to initial treatment. Median age at transplant was 52 years and the median time from diagnosis to transplant was 10 months. Median CD34+ cells obtained post mobilization was 5.30x106/kg (1.10-51.49x106/kg) in G-CSF arm and 12.50x106/kg (2.78-94.52x106/kg) in the GM-CSF arm (p=0.1). Engraftment (ANC >500/mul) occurred at a median of 10 days (8-13 days) in the G-CSF arm and 9 days (2-52days) in the GM-CSF arm (p=0.06) . Platelet recovery was prompt at 14 days (8-365) in the G-CSF arm versus 18 days (10-86) in the GM-CSF arm (p=0.03). Response, overall and disease free survival were similar in both cohorts. Overall, 39% of the patients achieved CR following priming chemotherapy which improved to 50% post transplant. Additional 35% of patients attained a PR post transplant for a total response rate of 85%. After a median follow-up of 1.64 years (0.03-6.6 years) 61% of patients relapsed or progressed. The median time to progression was 1 year post transplant (0.06-5.05 years). The overall survival was 86% (76%-96%) at one year, 73% (60%-86%) at 1.6 years, and 56% (40%-73%) at 3 years post transplant. Relapse or progression free survival of 68% (54%-81%) at 1 year, 50% (34%-66%) at 1.6 years and 36% (20%-53%) at 3 years was seen. 2 early transplant related deaths were seen. (VOD + intracranial bleed; RSV pneumonitis). 3 (5.5%) patients developed significant toxicities associated with priming chemotherapy. (Parainfluenza + renal failure; aspergillus and MI). 4 (7.4%) patients developed secondary MDS at a median of 1.4 years (1-2 years) post transplant. Conclusion: Mobilization with chemotherapy + G-CSF versus GM-CSF results in similar CD34+ progenitor cell counts. Early engraftment was seen with both. High dose therapy with autologous stem cell transplant improved CR rates.

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DIALOG(R)File 5:Biosis Previews(R)

0014397668 BIOSIS NO.: 200300356387
Characterization of the Short Term Repopulating Activity of Cultured Human Peripheral Blood Stem Cell Transplants Using Quantitative Assays in Mice and Clonal Analysis of Retrovirally Marked Cells in Patients.
AUTHOR: Glimm Hanno (Reprint); Schmidt Manfred (Reprint); Wissler Manuela (Reprint); Klingenberg Silke (Reprint); Waller Cornelius F (Reprint); Eaves Connie J (Reprint); Kalle Christof von (Reprint)
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ABSTRACT: The establishment of experimental methods for predicting clinical hematologic recovery kinetics after transplantation of manipulated human cell populations remains an outstanding unresolved issue. Human cells with myeloid-restricted short term repopulating activity (STRC-M) and lympho-myeloid but also short term repopulating activity (STRC-ML) consecutively contribute >90% of the human hematopoiesis seen after 3 and 8 weeks, respectively, in sublethally irradiated NOD/SCID-b2m-/- mouse hosts, but engraft NOD/SCID mice much less efficiently (JCI 2001; 107: 199-206). We have now determined how STRC-M and/or STRC-ML numbers change in cultures of mobilized peripheral blood (mPB) cells and compared the values obtained to hematologic recovery rates in patients transplanted with these cells. 1.3 - 3.9 x 106 CD34+ cells/kg from 6 patients with advanced malignant diseases were cultured for 3 days in serum-free medium with either flt-3 L, SF and IL-3 or flt-3 L, SF, IL-3, IL-6 and G-CSF. Expected changes were seen in total cells, CD34+ cells, CFC (all apprx2-fold increased) and in LTC-IC (apprx2-fold decreased). WBC recoveries (to >1000 /mul) after transplantation of these cultured cells were similar to historical control recipients of non-cultured cells (median = 10 days, range of 8-14). Platelet recoveries (to >20,000 /mul without platelet transfusion for 48h) were slightly delayed (median = 14 days, range of 9-%28%). For 3 of 4 of these samples, both STRC-M and STRC-ML decreased (9-fold and 3-fold, respectively) during culture. However, in the 4th they both increased and the patient transplanted with these cells showed the fastest leukocyte recovery. A study of the engraftment kinetics in 3 CML patients transplanted with autologous mPB cells marked genetically under similar culture conditions using a PG13/LN vector (after IRB, state and national review commission approval) allowed short-term clones regenerated in patients to be visualised. 8-25% of the CD34+ cells, 13-24% of the CFC and 9-13% of the LTC-IC were marked. Although only 8 to 25% of the autotransplants were placed in the transduction cultures, marked PB cells were detected 11 days post-transplant in all 3 patients. In 2, marked cells disappeared almost completely and permanently by 4 wks. In the third patient, a second wave of marked cells was seen after 3-4 months. Semiquantitative PCR demonstrated 0.1-1% marked PB cells during the first month post-transplant indicating up to 10% marking of STRC active in patients.

LAM-PCR showed multiple marked clones contributed to this early reconstitution. These findings indicate that a subpopulation of transplantable human cells important to early hematologic recovery in patients exists; that these cells can be assayed in mice, and that they can be efficiently transduced and their progeny detected in engrafted patients.

1/7/201
DIALOG(R)File 5:Biosis Previews(R)

0014397633 BIOSIS NO.: 200300356352
Infusion of High Numbers of G-CSF Mobilized Blood Dendritic Cells Type 2 (DC-2) Is Associated with an Increased Rate of Chronic GVHD in Allogeneic PBSC Transplantation.
AUTHOR: Arpinati Mario (Reprint); Chirumbolo Gabriella (Reprint); Urbini Benedetta (Reprint); Bonifazi Francesca (Reprint); Stanzani Marta (Reprint); Falcioni Sadia (Reprint); Bandini Giuseppe (Reprint); Tura Sante (Reprint); Baccarani Michele (Reprint); Rondelli Damiano (Reprint)
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ABSTRACT: It was previously shown that dendritic cells type-2 (DC-2) are significantly increased in G-CSF-mobilized leukapheresis products as compared to unstimulated bone marrow. In this study, we analysed whether the numbers of DC-1 and DC-2, as well as of other cell components in the graft, were associated with acute and/or chronic GVHD in 31 adult patients (11 MM, 7 CML-CP, 6 AML, 5 NHL, and 2 MDS) receiving an allogeneic PBSC transplant from HLA-matched siblings. Average cell doses (x10
6/kg) in the grafts were the following: 283+-137 CD3+ T cells, 160+-88 CD4+ T lymphocytes, 116+-55 CD8+ T lymphocytes, 64+-39 CD19+ B lymphocytes, 51+-29 CD56+ NK cells, 253+-103 CD14+ monocytes, 6.6+-4.1 CD34+ cells, 2.1+-0.9 HLA-DR+lin-CD11c+ DC-1 and 2.9+-1.3 HLA-DR+lin-CD123+ DC-2. Median follow up was 255 days (range: 50-685). Patients were initially divided in three groups according to whether they had shown no signs of acute GVHD (grade 0, n=10), acute GVHD grade I (n=12), or grade II - IV (n=9). Median numbers of CD34+ cells, lymphocyte subsets, and DC-1 and DC-2 received by patients in these three groups did not differ significantly. Of 21 patients with adequate follow up (median 485 days, range: 131-695) 12 developed chronic GVHD (10 extensive, 2 limited). Analysis of cell components of the grafts demonstrated that patients developing chronic GVHD had received a significantly higher dose of DC-2 than patients without chronic GVHD (3.3+-1.5 vs 2.2+-0.9, p=0.05), while the dose of DC-1 (p=0.7), monocytes (p=0.%28%), T lymphocytes (p=0.643), B lymphocytes (p=0.939), NK cells (p=0.487) and CD34+ cells (p=0.757) was not different. Also, chronic GVHD did not correlate with recipient or donor age or gender, interval between diagnosis and transplant, presence of ATG or TBI in the conditioning regimen, or type of GVHD prophylaxis. Our results suggest that the presence of large DC-2 numbers in the graft may be associated with a higher risk of chronic GVHD after allogeneic PBSC transplantation. These data might prompt further studies addressing whether depletion of graft DC-2 might be beneficial in this setting.

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DIALOG(R)File 5:Biosis Previews(R)

0014397612 BIOSIS NO.: 200300356331
Growth Factor Mobilized Peripheral Blood Stem Cell Collections from CML Patients in Complete Cytogenetic Remission on Imatinib Mesylate (Gleevec)Treatment Are Ph- by Standard Criteria but Are Contaminated with BCR/ABL+ Progenitor Cells.
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ABSTRACT: Treatment with imatinib mesylate (Gleevec) results in complete cytogenetic remission (CCR) in a high proportion of chronic myeloid leukemia (CML) patients.However it is not clear whether responses to imatinib will be durable. Peripheral blood stem cells (PBSC) collected from patients while in CCR may provide a source of BCR/ABL -ve stem cells for autologous transplantation in case of subsequent relapse. We have initiated a clinical trial to investigate whether BCR/ABL -ve PBSC can be mobilized using growth factor administration from patients in CCR (Ph -ve on karyotyping and BCR/ABL +ve cells within normal limits on FISH) on imatinib treatment. PBSC were collected from 10 patients (8 CP, 2 AP; median time from diagnosis to mobilization: 42 months (range 11-90 months); median duration of imatinib treatment: 18.5 months (range 11-27 months)). Patients received G-CSF (10mug/kg/day), and PBSC collection was initiated on day+5 with a minimum target cell dose of 2x106 CD34+ cells/kg. Imatinib treatment was continued during G-CSF administration and PBSC collection. The median number of CD34+ cells (106/kg) collected was 2.51 (0.69-4.27) with a median of 3 phereses collections(range 1-13). The target number of CD34+ cells was reached in 9 of the 10 patients. One patient, who was 90 months from diagnosis and and had received >5 years of prior interferon treatment, collected only 0.69x106CD34+ cells/kg after 4 phereses and refused further collection. The number of CD34+ cells collected correlated inversely with time from diagnosis (r=-0.65, p<0.05) but not with duration of prior imatinib treatment. PBSC were Ph -ve on karyotyping and with BCR/ABL +ve cells within normal background limits on FISH in 8 of 9 evaluable patients. One patient had Ph +ve, BCR/ABL +ve cells in 1of 13 phereses collections. Unrelated Ph- abnormal clones (insertion (3;4) and +22 in Ph -ve cells) were detected on karyotypic analysis of PBSC collections from 2 patients. The abnormal clones were not detected on prior bone marrow examination. We have previously shown that persistent BCR/ABL+ CD34+ progenitor cells can be detected in imatinib-responsive patients in CCR by standard criteria (Blood 2001, 98,11 suppl 1: 771A). We evaluated whether BCR/ABL+ progenitors could be detected in PBSC products collected in this study. CD34+ cells were isolated from PBSC products and analyzed for BCR/ABL by FISH. BCR/ABL+ cells were detected in PBSC collections from all 8 patients evaluated (median 9.8%, range 4.1-20) and in %17% of 19 evaluable pheresis products. BCR/ABL+ cells were also detected in colonies generated after plating of CD34+ cells in CFC and LTCIC cultures indicating that BCR/ABL+ CD34+ cells retained functional committed and primitive progenitor capacity. These results support the feasibility of collection of PBSC products from patients in CCR with imatinib treatment which are Ph -ve by standard criteria. However additional strategies to further deplete persistent BCR/ABL+ progenitors from PBSC collections need to be explored.

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DIALOG(R)File 5:Biosis Previews(R)

0014388206 BIOSIS NO.: 200300346925
Allogeneic Peripheral Blood Stem Cell Transplantation for the Treatment of Leukemia: A New Regimen for Acute GVHD Prophylaxis.
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ABSTRACT: Allogeneic hematopoietic stem cell transplantation remains to be the most effective therapy for the treatment of leukemia. To evaluate the efficacy of allogeneic peripheral blood stem cell transplantation (allo-PBSCT) in the treatment of leukemia and the regimens for prevention of acute and chronic GVHD, we performed allo-PBSCT in 50 patients with leukemia, 29 with acute leukemia (AML in CR1=16, CR2=1, ALL in CR1=13, CR2=4 and relapsed=2) and 21 patients with chronic myeloid leukemia (all in CML-CP). HLA-A, -B and -DR loci were matched in 47 donor-recipients and 1 locus mismatched in 3 donor-recipients. ABO blood types were matched in 30 cases and mismatched in 20 cases. PBSC were mobilized with G-CSF (lenograstim) 5 microgram/kg for 5 days. Conditioning regimens included standard TBI plus CTX or TBI plus CTX and VP16. Two regimens were used for prophylaxis of aGVHD, one was the standard combination of low dose cyclosporine (CsA, 2-3 mg/kg.d) and short course methotrexate (MTX, 15 mg for day 1 and 10 mg for days 3, 6 and 11) (CsA/MTX group), the other was short course mycophenolate mofetil (MMF, 1 g, q12h from day +1 to day +%28%) besides CsA and MTX with MTX of day 11 omitted (MMF/CsA/MTX group). All patients were successfully engrafted. The recovery of hemoglobin to 80 g/L independent of transfusion was significantly slower in ABO mismatched patients (median 52d) than that of ABO matched patients (median 15d) (p<0.05), while the recovery of counts of granulocytes and platelets were without significant difference (P>0.05). The incidence of aGVHD in the whole group was 40% (20/50) with 18% (9/50) of grade IIapprxIV. cGVHD occurred in 25 out of 35 patients (71.43%) who survived longer than 6 months post-transplantation with 12 extensive cGVHD (34.29%). The incidence of aGVHD in MMF/CsA/MTX group (16.67%, 3/18) was significantly lower than that of CsA/MTX group (53.13%, %17%/32) (P<0.05). Only 1 out of 18 (5.56%) patients of MMF/CsA/MTX group developed grade II aGVHD, while 8 out of 32 patients of CsA/MTX group developed grade II to IV aGVHD. Although the overall incidence of cGVHD was similar in two groups (72.73%, 16/22 vs 69.23%, 9/13, P>0.05), the incidence of extensive cGVHD was lower in MMF/CsA/MTX group (15.38%, 2/13) than that in CsA/MTX group (45.45%, 10/22) (p<0.05). The median follow-up duration was 30 months. The survival rate at 12 months post transplantation were 85.7% and 61.5% for MMF/CsA/MTX group and CsA/MTX group, respectively. GVHD, infection and interstitial pneumonitis were the main causes of death. In conclusion, allo-PBSCT is a safe and effective therapy for leukemia. The MMF/CsA/MTX regimen is more efficient for prevention of aGVHD than CsA/MTX.

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DIALOG(R)File 5:Biosis Previews(R)

0014380507 BIOSIS NO.: 200300337250
High Dose Therapy (HDT) and Autologous Peripheral Blood Stem Cell (PBSC) Transplantation as Salvage Treatment in HIV-Associated Lymphoma (HIV-Ly).
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ABSTRACT: The introduction of highly active antiretroviral therapy (HAART), by restoring the immune system defect in HIV-positive patients (pts), has allowed the evaluation of aggressive therapeutic approaches in HIV-Ly. We started a program of PBSC mobilization and collection, with subsequent HDT and transplantation as salvage therapy for pts with refractory or relapsed HIV-Ly. Inclusion criteria were availability of effective HAART and absence of active opportunistic infections (OI) or CNS lymphoma. Pts with previous AIDS-defining OI were included. Eligibility for HDT included sensitivity to 1/more courses of second-line standard-dose CT. Up to July 2002, 10 pts entered the program, 7 with HD (three 1st relapse, two 2nd relapse, two refractory) and 3 with NHL (1st relapse). Median age was 38 (31-56), median CD4 count 158/cmm (%17%-451), disease stage II (1), III (3) and IV (6) (marrow in 4). Two pts had detectable HIV-viremia and 5 had chronic HCV hepatitis. First-line CT was Stanford V (6 pts) and EBVP (one pt) in HD and CDE, CHOP and ACVBP in NHL. Median duration of last complete remission (CR) was 6.5 months (mo) (range 1-53). After a median of 3 (2-3) apheresis, a median of 5.9 (range 4.1 - 8.3) x 106/Kg CD34+ cells were collected, after cyclophosphamide 4 gr/sqm + G-CSF in 2 or G-CSF-supported standard-dose CT in 5 cases. One pt with refractory HD and bone marrow involvement died soon after second-line treatment for disease progression; two pts failed to mobilize after either second-line CT and cyclophosphamide. One pt had progressive HD soon after PBSC collection and died. Six pts (60%) underwent HDT with BEAM (BCNU 300mg/mq, VP16 200mg/mq x 4, Ara-C 200mg/mq x 4, Melphalan 140mg/mq) and PBSC transplantation. Prompt hematologic recovery was observed in all pts (PMN>500/cmm at +10 (range 8-10) and self-supporting plts>20.000/cmm at +13 (range 11-18). Treatment-related toxicities included two WHO 3 and one WHO 2 oral mucositis and one WHO 3 reaction to DMSO. Infectious complications during neutropenia included one WHO 3 facial cellulitis, one WHO 3 staphylococcus epidermidis sepsis and WHO 2 clostridium colitis; all pts responded well to treatment. HIV viral load remained undetectable in 3/4 pts who received HAART before and after transplant; in one pt 1400 copies/ml were detected after 5 mo. No HCV reactivations were seen. Opportunistic infections were seen in 3 pts and all responded promptly to treatment: a varicella zooster infection at 5 mo and an esophagus candidosis at 9 mo in 1 pt; a varicella zooster infection at 3 mo in a pt and an esophagus candidosis at 9 mo in 1 pt. 5/6 pts achieved CR and three are currently alive and disease-free 2, 3 and 9 mo after transplant. Relapse occurred in two pts, 5 and 12 mo after transplant. In conclusion, adequate numbers of CD34+ cells can be collected in most HIV+ pts even though with advanced lymphoma and after intensive first-line CT. HDT with PBSC transplant is feasible, with rapid hematologic recovery and acceptable toxicity. The impact on HIV infection seems mild in pts on HAART. Clinical results are promising, considering the poor prognostic features of this unselected series.

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DIALOG(R)File 5:Biosis Previews(R)

0014380483 BIOSIS NO.: 200300337226
Autologous Stem Cell Transplantation (ASCT) in 419 Patients with Follicular Lymphoma (FL).
AUTHOR: Conde Eulogio (Reprint); Insunza A (Reprint); Lahuerta J J (Reprint); Sureda A (Reprint); Caballero D (Reprint); Arranz R (Reprint); Marco F (Reprint); Garcia-Conde J (Reprint); Carreras E (Reprint); Vidal

M J (Reprint); Gandarillas M (Reprint); Leon A (Reprint); Bermudez A (Reprint); Zuazu J (Reprint); Fernández-Sevilla A (Reprint); Garcia-Larana J (Reprint); Gonzalez-Ponte L (Reprint); Carrera D (Reprint); Giraldo P (Reprint); Rodriguez J (Reprint); Grande C (Reprint) ; Palomera L (Reprint); Cabrera R (Reprint); Varela M R (Reprint); Perez-Equiza C (Reprint); Moraleda J M (Reprint); Hernandez F (Reprint); Iriondo A (Reprint); Rifon J (Reprint); Bello J L (Reprint); Albo C (Reprint); Garcia-Ruiz J C (Reprint); Vela J A Garcia (Reprint); Nieto L Hernandez (Reprint); Fernandez-Ranada J M (Reprint); Miguel J San (Reprint); Sierra J (Reprint); Unin A Zubizarreta Hospital (Reprint)
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ABSTRACT: A retrospective analysis was performed to investigate the outcome of ASCT in 419 patients (pts) with FL and reported to the GEL/TAMO database between June 1987 and July 2002. There were 211 males and 208 females with a median age of 46 (30-62) years. Cases had been classified according to WF as follicular small cleaved cell 153, follicular mixed 202 and follicular large cell 64 and most of them reclassificated according to the criteria of the REAL. Most pts transplanted in1st CR fulfilled bad prognostic criteria. Chemotherapy regimens used as first-line therapy were CHOP in 282 pts (67%), CVP in 39 pts (9%), ProMACE-CytaBOM in %28% pts (7%) pts, FMD in 15 pts (4%) and other regimens in 55 pts (13%). Tumor response after 1st line chemotherapy was CR in 282 pts (67%), PR in 126 pts (30%) and failure in 11 pts (3%). Disease status at ASCT was 1st CR in 112 pts, 2nd CR 108 pts, sensitive disease (SD) in 180 pts and resistant disease (RD) in 45 pts. Stem cells for engrafment were obtained from BM in 90 cases (21%) and from PB in the remaining 329 (79%). To mobilize PBSC 138 pts received G-CSF, 179 G-CSF plus chemotherapy and 12 only chemotherapy. The median number of CD34+ cells infused was 3.12 x106/kg (range 0.9 to 14.3). The conditioning regimen was CY+TBI in 99 pts (24%), BEAM in 183 ts (44%), BEAC in 107 pts (25%), CBV in 23 pts (5%) and other in the remaining 7 pts (2%). Response after transplantation was CR in 363 pts (87%), PR in 29 (7%), failure of treatment in 19 (4%) and the other 8 pts (2%) were not evaluable because they died before the engrafment. The median follow-up was 32 months (range 3-148). One hundred and six pts (29%) have relapsed, the median time to relapse was 16 months (range 3-92). Actuarial 12-year OS and DFS were 61% (95% CI: 53-69%) and 37% (95% CI: 27-47%), respectively. The actuarial probability of relapse for 363 evaluable pts was 49% (95% CI: 39-59), at 12 years. In univariate analysis, prognostic parameters associated with DFS were symptoms at diagnosis (p<0.006), PS status at diagnosis (p=0.01), IPI at diagnosis (p=0.006) and status of disease at ASCT (p<0.00005). In multivariate analysis, status of disease at ASCT was the best predictor factor for DFS (2nd CR (RR 2.3; 95% CI: 1.2-4.3), SD (RR 5.4; 95% CI: 3.1-9.5), RD (12.1; 95% CI: 5.6-25.8), p<0.00005). Status of disease at ASCT was, also, the most important factor for relapse (p=0.009). There were 12 occurrences of secondary neoplasm yielding and an estimated incidence of 8% (95% CI: 4-12%) at 97 months. Ninety eight pts (23%) died. Sixty one (15%) died because of lymphoma and the remaining 37 (8%) died due to toxicity. ASCT is a therapeutic option in pts with FL in remission or sensitive disease. The procedure was well tolerated with an acceptable toxicity, but longer follow-up is needed to evaluate the impact on survival. Relapse is the principal cause of failure of treatment.

0014380464 BIOSIS NO.: 200300337207
CD6-Negative Mobilized Blood Cells Facilitating HLA-Haploidentical Marrow Transplantation for the Treatment of High Risk Hematopoietic Neoplasia.
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ABSTRACT: Stem cell transplants from family members sharing one HLA-haplotype and differing in 0 - 3 HLA-antigens (A, B, DR) of the second haplotype carry a high risk of rejection and graft-versus-host disease. Pretransplant conditioning consisted of total body irradiation, buffy coat transfusion from the prospective marrow donor, antithymocyte globulin and cyclophos-phamide. Post-transplant cyclosporine A and methotrexate was given routinely for prevention of graft-versus-host disease (GvHD). We have studied the use of CD6-negative mobilized blood cells (MBC) 6 days after marrow transplantation for facilitating engraftment of hap-loidentical marrow transplants without GvHD. G-CSF mobilized blood cells (MBC) depleted of CD6-positive T-cells by immunomagnetic bead depletion suppressed the mixed leukocyte culture between HLA-mismatched individuals. Suppression was exhibited by the CD8-positive subset of CD6-negative cells and suppression was abrogated by the depletion of CD8-positive cells. CD8 positive cells were T cell receptor (TCR) gamma-delta negative and in part TCR alpha-beta positive. 36 patients were grafted with marrow and CD6-negative MBC for advanced leukemia (refractory AML %17% patients, ALL 10 pats., CLL 2 pts., MDS 1 pt., advanced CML 2pt., refractory NHL 4 pt.). HLA-antigen differences of the donor (host-versus-graft direction) involved 3 antigens in 9, 2 antigens in 13, one antigen in 11 and no antigen in 3 pts. In the GVH direction 3 antigens were involved in 8, 2 antigens in 12, one antigen in 11 pts. and no antigen in 5 pts. 23 patients were male and 13 female, the median age was 36 years (range %17% - 53). Four pts. died early and were excluded from further evalua-tion. 32 pts. showed full engraftment. GvHD was mild in 9 pts., moderate in 7 pts. and severe in one given CD6-negative MBC. The 2 year actuarial survival (OS) is 19.2 %, the relapse rate (RR) 56 % and the transplant-related mortality (TRM) 36 %. Causes of deaths were re-current disease in 11 pts., infections (4 viral, 5 fungal, 1 mycoplasma), pulmonary failure and bronchiolitis. The results were better in pts with early disease (OS 75%, RR 25%, TRM 0%). We conclude from our study that CD6-negative, CD8-positive cells facilitate engraftment of HLA-haploidentical stem cell transplants in pts. with high risk hematopoietic neoplasia. However infections present therapeutic problems. Future attempts will be directed to trans-plantation at an earlier stage of the disease and better prevention of infections by improving immune reconstitution.

0014380463 BIOSIS NO.: 200300337206
Transplantation of CD133+ Selected Haploidentical Hematopoietic Stem Cells.
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ABSTRACT: Here we present first clinical results on combined use of positively selected CD133+ and CD34+ hematopoietic stem cells in a haploidentical stem cell transplantation setting. Preclinical studies show that positively selected CD133+ stem cells have a greater potential for engraftment than positively selected CD34+ stem cells. Therefore, the feasibility of adding positively selected CD133+ cells to CD34+ grafts prepared with the CliniMACS-system in the haploidentical transplantation setting was investigated. Five patients (1 secondary myelomoncytic leukemia, 1 cALL in CR3, 1 Wiskott-Aldrich syndrome and 2 T-ALL in CR1) were transplanted with G-CSF mobilized peripheral blood stem cells from HLA-haploidentical related donors (n = 5). Median of age was 10.2 years (1 to 18 years). Conditioning regimens were based either on busulfan or total body irradiation. Patients received a median of 21.4 x 10
6 (6.6 to 27.9 x 10
6) CD34+ selected cells and a median of 5.8 x 10
6 (1.5 to 12.2 x 10
6) CD133+ selected cells per kg of body weight with only 2.5 x 10
4 contaminating T cells/kg. The first three patients received anti-thymocyte globuline (ATG, d-3 to d-1) and OKT3 (d+1 to d+15) as rejection prophylaxis and G-CSF application. Two other patients received only ATG for rejection prophylaxis and no G-CSF application. No GvHD greater than grade I occurred. Causes of death were adenoviral infection and aspergillosis in two patients (day+36 and day+115) and leukemic relapse in one patient (day+194). Two patients are alive and well day+112 and day+186 post transplant. Median time to reach more than 500 neutrophils with or without G-CSF was 10.3 days vs. 31 days. All five patients showed rapid recovery of platelets. Median time to platelet take with a platelet count greater than 20.000/mul was %17%.2 days and greater than 50.000/mul was 20.2 days. Our preliminary data show that addition of CD133+ selected stem cells may enhance platelet recovery in the context of haploidentical transplantation. These preliminary data may provide the basis for exclusive use of CD133+ cells in haploidentical transplantation.

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DIALOG(R)File 5:Biosis Previews(R)

0014380458 BIOSIS NO.: 200300337201
Effective Universal Outpatient Immunotherapeutic Approach for Refractory Acute Myelocytic Leukemia: HLA-Haploidentical Transplants in 100cGy-Conditioned Hosts.
AUTHOR: Colvin Gerald A (Reprint); Lambert Jean-Francois (Reprint); Lum Lawrence G (Reprint); Rathore Ritesh (Reprint); Falvey Mary (Reprint); Abedi Mehrdad (Reprint); Quesenberry Peter J (Reprint); Elfenbein Gerald J (Reprint)
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ABSTRACT: We previously studied allogeneic BMT with HLA-identical sibling donors using 100cGy as host conditioning and infusing 1x108 CD3+ cells/kg from non-mobilized PB and achieved an impressive response with complete responses in 4 of 11 refractory hematologic malignancies patients (Blood 100:442, 2002). Responding patients were transiently or permanently chimeric. Around 25% of eligible patients for allo-BMT have an HLA-identical sibling donor and this number is considerably less in older patients, however, nearly 100% have HLA-haploidentical donors, making this an attractive area of investigation. In addition, many patients are too old or ill to tolerate a standard or non-myeloablative allo-BMT. We evaluated haplo-BMT response and toxicity with CD3+ cell dose escalation in those with refractory malignancies. We performed %28% haplo-BMT. The CD3+ cell dose ranged from 1x106-2x108 cells/kg infused with 2-4x106 CD34+ cells/kg (goal 4x106). G-CSF primed PBSC, with a conditioning regimen of 100cGy TBI on day 0, was used. Median age was 58(16-82). Diagnoses included: AML(4), NHL(5), MM(4), bladder(3), breast(3), H(1), renal(2), Ewing's(2), MDS(1), lung(1), melanoma(1), and prostate cancer(1). One treatment related death (3%) occurred from grd-IV AGVHD (bowel perf.) in a haplo-patient with 100% chimerism. Most had a transient febrile syndrome termed haplo-immunostorm (described separately) at high CD3 cell levels. All had pancytopenia, lasting a median of 22 days, with a nadir at apprx4 wks which was deeper and longer when gtoreq1x108 CD3+ cells/kg infused. There were 2 febrile neutropenia admissions (7%). Three major clinical responses occurred, all in absence of measurable donor chimerism (<5%). All responses occurred at CD3 levels of 1-2x108 cells/kg. Fourteen patients received these levels of CD3+ cells. There were 3 responses in the 4 patients with myeloid malignancies. The 4th patient died 2 wks after haplo-BMT with an overwhelming fungal infection. All 3 evaluable patients who had AML achieved a complete response. One patient with refractory APL and persistent blasts after re-induction chemo underwent haplo-BMT. He cleared all measurable leukemia and was PCR neg. for the 15:%17% translocation at day 60+. Two had AML in the setting of MDS. Although both patients cleared their leukemic clones, they were left with their underlying MDS. One patient was free of blasts 195+ days out from initial BMT, but lost all megakaryopoiesis and had a second haplo-BMT day 173+. He succumbed from bleeding after refusing further supportive care. The other with residual MDS initially lost 2 of 3 cytogenetic clones with retention of 5q-. Further clonal-evolution occurred with development of recurrent AML with different cytogenetics day182+. In summary: 1) low dose TBI of 100cGy followed by haplo-BMT is a biologically active therapy that can eradicate evidence of far advanced disease, 2) tumor response occurred outside of detectable chimerism, 3) this is a well tolerated outpatient treatment that produced minimal toxicity for the majority of patients, and 4) this is the first report of successful outpatient haplo-BMT achieving several clinical responses for patients with end stage, refractory malignancies. Theories on biological effect include an initial graft vs. tumor cell kill, altered host immune response breaking host tumor tolerance, persistent non-detectable microchimerism or a combination of the three.

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DIALOG(R)File 5:Biosis Previews(R)

0014380403 BIOSIS NO.: 200300337146
Haplo-Identical Stem Cell Transplantation (SCT) with Standard Dose Purified CD34+ Cells and a Chemotherapy-Alone Conditioning Regimen Followed by Donor Leukocyte Infusion (DLI).
AUTHOR: Lacerda Joao F (Reprint); Martins C; Carmo J A; Lourenco F; Juncal C; Rodrigues A; Vilalobos I; Moura M C; Lacerda J M F
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ABSTRACT: Most protocols of haplo-identical SCT use irradiation-containing conditioning regimens and infuse mega doses of CD34+ cells. In this setting, we investigated whether standard doses of purified CD34+ cells could induce durable donor engraftment after a chemotherapy-alone conditioning regimen, as well as the role of a limited dose of DLI in the prevention of disease relapse. Our regimen consisted of thiotepa 5 mg/kg/day D-9 and D-8, fludarabine 40 mg/m2/day D-9 to D-5, rabbit ATG 5 mg/kg/day D-7 to D-3, melphalan 60 mg/m2/day D-4 and D-3, cyclosporin 3 mg/kg/day D-10 to D-2, and prednisolone 2 mg/kg/day D-7 to D-3. PBSCs were mobilized with G-CSF 10-12 mcg/kg/day for 5 days and standard volume leukapheresis were performed on days 4 and 5. Two donors had 3 leukapheresis. Each product was processed individually in the CliniMACS system and cryopreserved. Since October 1998, a total of 13 pts (7 males, 6 females) with a mean age %28%.23 +- 12.08 years were treated. The diagnoses were AML (n=9), acute biphenotypic leukemia (n=2) and CML (n=2). Of the 9 pts with AML, 2 were primary refractory, 2 secondary to MDS, 4 had relapsed after an AutoSCT and 1 had a resistant relapse. One pt with acute biphenotypic leukemia had a resistant relapse. One of the pts with CML had accelerated disease and the other was in second blastic phase. Twelve of the 13 donor-patient pairs shared 3/6 HLA antigens and 1 pair shared 5/6 HLA antigens. The pts received a median of 5.4 (2.9-13.8) x 10.6 CD34+ cells/kg, 1.62 (0.33-5.96) x 10.4 CD3+ cells/kg and 9.32 (5.5-12.55) x 10.4 CD19+ cells/kg. T-cell depletion was the only GVHD prophylaxis. G-CSF was administered post-transplant. All 13 pts had engraftment; the median day of neutrophils above 500/mcl was D11 (D11-D20) and that of platelets above 20000/mcl was D19 (D13-not reached). Donor cell engraftment was confirmed by DNA quimerism studies on D21 to D30; one pt with primary resistant AML had 92% donor cells on D21 and relapsed shortly thereafter. The toxicity of the conditioning regimen was minimal. All surviving pts received at least one infusion of donor whole blood containing 5.0, 10.0, 25.0 or 50.0 x 10.3 CD3+ cells/kg between D25 and D95 post-transplant. Of the 9 evaluable pts, 6 developed AcGVHD (2 GI, 2 GII, 1 GIII, 1 GIV), 1 also developed a mild BOOP-like syndrome, and 2 pts developed a BOOP-like syndrome alone (1 moderate, 1 severe), a median of 47 (27-101) days after DLI. Five of the 6 pts with AcGVHD recovered fully with immunosuppressive therapy. One pt with AML in relapse post-transplant had extensive skin AcGVHD after several DLI, was not treated, but died of progressive leukemia. With this exception, all other pts developing AcGVHD survive disease free more than 692 days post-transplant, off immunosuppressive therapy. As of August 2002, 7/13 pts survive a median of 996 (69 to 1208) days post-transplant with 100% donor cells. Our observations demonstrate that durable full donor engraftment is possible in the setting of haplo-identical related SCT with the infusion of standard dose purified CD34+ cells following a highly immunosuppressive chemotherapy-alone conditioning regimen.

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DIALOG(R)File 5:Biosis Previews(R)

0014380402 BIOSIS NO.: 200300337145
Contribution of T Cells to Engraftment: A Comparison of T Cell Depleted vs. T Cell Replete Allografts after Reduced-Intensity Conditioning.
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ABSTRACT: Reduced-intensity (RI) conditioning regimens permit engraftment of T cell replete (TCR) allografts with varying degrees of donor chimerism. Factors that influence engraftment include host immune status, histocompatibility, hematopoietic "space", stem cell dose, and T cell dose within the allograft. We previously demonstrated that sequential, immune-depleting chemotherapy permits rapid and complete engraftment of TCR allografts. To determine the contribution of allograft T cells to engraftment, patients (pts) receiving TCR allografts (n = 19) were compared to pts receiving T cell depleted (TCD) allografts (n = 10) after RI conditioning. To control for host immune status all pts received 1-3 cycles of induction immune-depleting chemotherapy at conventional doses with the goals of reducing circulating CD4 counts < 50/mm3 and providing tumor control prior to transplant. Median CD4 counts after induction were TCR = 60 (12-191) vs. TCD = 44 (19-90) (p = 0.26). Pts then received an identical RI conditioning regimen of cyclophosphamide 1.2 gm/m2/d and fludarabine 30 mg/m2/d x 4 days. All pts received G-CSF mobilized blood allografts from HLA-matched sibling donors. To control for stem cell dose, all pts received a minimum of 4 x 106 CD34+ cells/kg. Median CD34+ cell doses (106/kg) were similar: TCR = 7.53 vs. TCD = 6.64. TCR pts received a median of T cell dose of 3.63 (1.53-8.%28%) x 108 CD3+ cells/kg. T cell depletion was performed with CD34 positive-selection and a panel of monoclonal antibodies against CD2, CD6, and CD7 resulting in a 4-5 log depletion. T cell doses were adjusted so that all TCD pts received 1 x 105 CD3+ cells/kg. All pts received full dose cyclosporine until day+%28%. Hematopoietic recovery times were similar between the two groups; median time to ANC > 1000: TCR = 9.0 (7-12) days vs. TCD = 9.5 (8-11) days and plt > 50K: TCR = 13.5 (9-31) days vs. TCD = 13.5 (8-18) days. All pts had evidence of early myeloid engraftment, and 18/19 TCR pts had complete lymphoid donor chimerism (>95%) at day+%28% post-transplant, using a VNTR-PCR assay. In contrast 5/10 TCD pts had donor lymphoid chimerism less than 95% (25 - 55%) at day +%28% post-transplant. All TCD pts converted to complete donor lymphoid chimerism after receiving planned, dose-escalated donor lymphocyte infusions on days +42, +70, +98 post-transplant. There were no graft rejections or failures in either group. Mixed lymphoid chimerism in the TCD group was inversely correlated with pre-transplant CD4 numbers (r = -0.762, p = 0.044). There was also an inverse trend to pre-transplant CD3 number (p = 0.059) and CD8 (p = 0.073) numbers, but not for NK numbers (p = 0.81). These data suggest that RI conditioning can permit the engraftment of TCD allografts from HLA-matched siblings with a minimum of 1 x 105 CD3+ cells/kg. In addition the data suggest that T cells within the allograft significantly contribute to lymphoid engraftment through a GVH mechanism directed against residual host immunity. These results may partially explain the complete lymphoid chimerism observed with TCR allografts. Optimization of host T cell depletion prior to transplant may be a strategy to enhance the engraftment of both TCR and TCD allografts with RI conditioning.

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DIALOG(R)File 5:Biosis Previews(R)

0014380167 BIOSIS NO.: 200300336910
Prophylactic Growth Factor Use in Older Patients with Previously Untreated Acute Myeloid Leukemia: A Published Data Meta-Analysis.
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ABSTRACT: Introduction: Poorer outcomes are observed in older patients with acute myeloid leukemia (AML), due in part to an increased risk of

treatment related mortality including development of life-threatening infections. In an attempt to reduce infection-related mortality and improve overall outcome, myeloid growth factors (GFs) have been used to hasten hematopoietic recovery. Randomized trials evaluating GFs in older patients have been published with conflicting results. To better define their role, we performed a published-data meta-analysis of randomized trials testing the use of GFs during induction chemotherapy in older patients with AML. Methods: A computer-based search of MEDLINE, CANCERLIT, Cochrane Library, PDQ, ASH and ASCO abstracts (1997-2001) and a manual search of references from published reports was performed. Randomized trials of prophylactic use of GFs compared to placebo or untreated controls in patients aged 50 years and older were identified. Trials reporting results of subsets of these patients were also included. Data abstracted included: chemotherapy regimen; GF type, dose and schedule; number of patients enrolled, randomized and evaluable; and results for each specified outcome. Outcomes evaluated included complete remission (CR), disease free survival (DFS) and overall survival (OS) at 2 years, number of infections and deaths due to infection, time to neutrophil (PMN) recovery of gtoreq0.5 x 109/L, days of antibiotic use, and days in hospital. Results: Eight randomized trials that included 1778 patients were identified. There were five trials of GM-CSF (1092 patients) and 3 trials of G-CSF (686 patients). Six of the trials included only older patients and 2 reported the results of a subset of older patients included in trials that also enrolled younger patients. Seven trials (1460 patients) were double-blinded, placebo-controlled and one (318 patients) included untreated controls. Using a random effects model, a meta-analysis did not detect a difference in outcome with the use of GFs over placebo with respect to CR rate (risk ratio (RR)=0.94; 95% confidence interval (CI):0.8-1.1; p=0.4), 2 year DFS (RR=0.88; CI:0.7-1.09; p=0.2), 2 year OS (RR=0.97; 95% CI:0.9-1.05; p=0.5), risk of infection (RR=0.99; 95% CI:0.91-1.07; p=0.7), or infectious death (RR=0.97; 95% CI:0.62-1.53; p=0.9). Six trials reported results on the impact of GF therapy on PMN recovery; 5 trials reported days in hospital; and 3 trials reported antibiotic use; reporting of median values for these results precludes pooling of these data. Time to PMN recovery ranged between 13-24 days for the GF groups compared with %17%-29 days for the control groups, and was faster with GFs in all trials. Time in hospital ranged between %28%-36 days for the treated groups and 29-38 days for the control groups. Antibiotic use ranged between 20-23 days for the treated groups compared with 16-26 days for the control groups. Conclusion: A meta-analysis of 8 randomized trials evaluating the use of GFs in older patients undergoing induction therapy for AML demonstrates that GF use hastens PMN recovery; no differences in the incidence of infections, infectious deaths, response rate, disease free survival or overall survival were detected.

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DIALOG(R)File 5:Biosis Previews(R)

0014380157 BIOSIS NO.: 200300336900
Salvage Chemotherapy with Fludarabine, Cytosine Arabinoside, DaunoXome and G CSF (FLAG X) in Heavily Pretreated Children and Adults with Relapsed Refractory Lymphoproliferative Malignancies. A Single Center Experience.
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ABSTRACT: BACKGROUND AND PURPOSE : Various chemotherapy regimens have been used in relapsed/ refractory lymphoproliferative malignancies. These high risk patients often need an allogeneic or autologous transplant for optimal benifit. In the subgroup of patients who have had multiple relapses or refractory disease and are therefore heavily pretreated, options for effective salvage chemotherapy to obtain remission or reduce disease bulk in order to progress to a transplant procedure are limited. Anthracycline related cardiotoxicity, especially in this heavily pretreated group, is a limiting factor. Liposomal Daunorubicin (DaunoXome) is thought to be less cardiotoxic but, atleast, equally effective. FLAG +/ - IDA is increasingly used in relapsed/ refractory myeloid malignancies.We have done a single arm pilot study using FLAG X in relapsed/ refractory myeloid and lymphoid malignancies. We present the response and toxicity in the lymphoid cohort. %17% patients (10 ALL, 7 NHL) were treated with a total of 23 cycles of FLAG X (30 mg/ m2 Fludarabine days 1-5, 2 gm/ m 2 Cytosine Arabinoside days 1-5, 80 mg/ m 2 DaunoXome Days 1-3, 300 micro gm G CSF daily). The median age was %28% years (range 5.5 - 62) and there was a total of 12 male and 5 female patients. 5 had primary refractory disease, 4 had relapsed disease, 7 relapsed/ refractory disease and 1 patient had FLAG X as the initial treatment in a high risk setting (ALL blast crisis on a background of CML). Among the %17% patients 10 had ALL and 7 had NHL. Subtypes of ALL included Common ALL (3), Pre-B ALL (3), T-ALL (3) and ALL blast crisis on a background of CML(1). Histological subtypes of NHL included transformed follicular lymphoma (4), T lymphoblastic lymphoma (4) and B non hodgkins lymphoma (1). RESULTS : Among %17% patients, complete remission (CR) was obtained in 11 (65%) and partial response (PR) in 1 (6 %) with an overall response rate of 71 %. Eleven of the twelve responders have proceeded to a transplant procedure (9 allogeneic / 2 autologous), 2 after FLAG consolidation. One died after FLAG consolidation before BMT could be done. One had DLI (relapse after prior BMT, remains in CR) and one was unfit for BMT (died with secondary AML one year later). Three of the seventeen (18%) had a minimal response and one patient died early (NE) with multi organ failure secondary to sepsis. After BMT 5 have subsequently relapsed and 4 died from infection. Median time to neutrophil (> 1000/ micro l) and platelet (> 20,000/ micro l) recovery were 23 days (range 14 - 44) and 22 days (range 14 - 30) respectively. Non haematological toxicity was modest. Long term follow up of cardiotoxicity is ongoing. CONCLUSION : The FLAG X regimen is a feasible and safe option for children and adults with relapsed refractory and high risk lymphoid malignancy. Remission was achieved in some patients refractory to multiple alternative courses of chemotherapy. It may be useful to consider this option at the time of first relapse in ALL and in selected, less heavily pretreated patients. The combination gave a high response rate in this heavily pretreated group allowing BMT in remission, but the final outcome suggests that this group require more intensive consolidation prior to BMT.

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DIALOG(R)File 5:Biosis Previews(R)

0014380056 BIOSIS NO.: 200300336799
Proto-Oncogene c-jun Expression Is Induced by AML1-ETO in a JNK-Dependent Manner: Possible Role in the Pathogenesis of Acute Myeloid Leukemia.
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ABSTRACT: Overexpression of proto-oncogene c-jun and constitutive activation of the Jun-N-terminal kinase (JNK) signaling pathway have been implicated in the leukemic transformation process. However, c-jun expression has not been investigated in acute myeloid leukemia (AML) cells with the most common chromosomal translocations. In t(8;21), the resulting AML1-ETO fusion gene has previously been shown to increase c-Jun phosphorylation in NIH3T3 cells, but the role of the JNK signaling pathway for the functional properties of AML1-ETO is unknown. In the present study we found high expression of c-jun mRNA in t(8;21), t(15;%17%) and inv(16) positive patient samples by microarray analysis. Within t(8;21) positive patient samples there was a positive correlation in the mRNA expression levels of AML1-ETO and c-jun. In myeloid U937 cells, c-jun mRNA and c-Jun protein expression increased upon induction of AML1-ETO. We found that AML1-ETO transactivated the human c-jun promoter through the proximal AP-1 site via activating the JNK signaling pathway. Interference with JNK and c-Jun activation by using JIP-1 or a JNK-inhibitor reduced the transactivation capacity of AML1-ETO on the c-jun promoter, and the pro-apoptotic function of AML1-ETO in U937 cells. G-CSF receptor neutralizing antibodies reduced phosphorylation of JNK in AML1-ETO expressing U937 cells suggesting that an autocrine loop mediated by G-CSF via the G-CSF receptor induces JNK activation. Thus, by altering cytokine receptor induced signaling pathways, AML1-ETO exerts positive effects on nuclear transcription factor activation and subsequent target gene expression.

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DIALOG(R)File 5:Biosis Previews(R)

0014380051 BIOSIS NO.: 200300336794
Transgenic Mice Expressing hCG-NuMA-RARalpha Develop Hematopoietic Abnormalities Leading to Acute Promyelocytic Leukemia.
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ABSTRACT: Acute promyelocytic leukemia (APL) is characterized by the accumulation of cells blocked at the promyelocytic stage of differentiation in the bone marrow of patients, and by the presence of a reciprocal chromosomal translocation involving retinoic acid receptor alpha (RARalpha). To date, five RARalpha partner genes have been identified in APL. The variant fusion gene NuMA-RARalpha was cloned by our group in 1996, from an infant case of APL carrying the translocation t(11;%17%)(q13;q21); we are thus interested in identifying the role of this variant fusion in the pathogenesis of APL. Using a construct containing the NuMA-RARalpha fusion gene driven by the human cathepsin G promoter (hCG-NuMA-RARalpha) two transgenic founder mice were generated and backcrossed with wild-type C57Bl/6 mice to generate F1 mice; presence of the hCG-NuMA-RARalpha transgene was confirmed by genotyping using PCR and Southern Blot. Mice were tail bled monthly and phenotyped by automated complete blood count, flow cytometry and manual differential counts of peripheral blood films. Animals were also sacrificed bimonthly for detailed examination of organ and bone marrow phenotypes. Transgenic mice displayed a mild leukocytosis and a persistent neutrophilia without chronic infection at >85% penetrance (18/21 mice older than 9 months), and elevated numbers of Gr-1positive/Mac-1positive cells. A subset of 33% (6/18) of these transgenic mice also exhibited multiple additional hematopoietic abnormalities in their peripheral blood, including the presence of promoyelocytes/blasts (>2% of cells counted), presence of >10% CD117positive cells and an abnormal population of Gr-1+/Mac-1+/CD117+ cells (onset >12 months). In addition, mice exhibited a severe leukocytosis, and mild anemia and thrombocytopenia. Data from analysis of bone marrow of wild-type and transgenic mice indicated a gradual accumulation of promyelocytes over time in transgenic mice. In leukemic mice, this cell population was evident via flow cytometric analysis, and possessed an immunophenotype very similar to human APL. Consistent with a blockade of neutrophil differentiation being evident in transgenic mice, hematopoietic progenitor cells from these animals were not responsive to G-CSF treatment, but responded partially to GM-CSF. These data indicate that, similar to other transgenic models of APL, hCG-NuMA-RARalpha transgenic mice acquire a nonfatal abnormal hematopoietic phenotype that develops into an APL-like disease.

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DIALOG(R)File 5:Biosis Previews(R)

0014379982 BIOSIS NO.: 200300336725
RalGDS as the Principal Molecule Responsible for the Block in Myeloid Differentiation Mediated by Oncogenic Ras.
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JOURNAL: Blood 100 (11): pAbstract No. 2027 November 16, 2002 2002
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ABSTRACT: Activating point mutations of Ras are one of the most common molecular abnormalities in adult myeloid leukemia and preleukemia (20-40% incidence). Constitutive activation of Ras also occurs through the loss of its negative regulator, encoded by the Neurofibromatosis Type 1 (NF1) gene product. NF1 mutations are present in up to 30% of all Juvenile Myelomonocytic Leukemia (JMML) patients. Using the mouse hematopoietic factor-dependant cell line, FDCP-mix, we have demonstrated that oncogenic Ras (Ras*) results in an increased hypersensitivity to GM-CSF and a block in neutrophil differentiation similar to that observed in JMML. The aim of this study is to elucidate the mechanism of the developmental block by identifying the key signaling molecules influencing neutrophil development downstream of Ras. The involvement of the following Ras effectors were examined: Raf, phosphoinositide 3 kinase (PI3K) and the Ral guanine nucleotide exchange factors (RalGEFs), RalGDS and Rlf each of which promote the activity of the small GTPase, Ral, when activated by Ras. In order to distinguish the contribution of these effector molecules to the block in neutrophil development we first employed effector loop domain mutants of Ras*, which selectively activate these downstream effectors. Stable expression of these mutant constructs in FDCP-mix cells was established by retroviral transduction. As is characteristic of the FDCP-mix line, cells containing empty vector underwent self-renewal in the presence of IL-3, but terminally differentiated over 7 days when cultured in the presence of G-CSF and GM-CSF giving rise predominantly to mature neutrophils (47%+-6) and giving a total 9-fold+-4 proliferative expansion. Expression of Ras* perpetuated proliferation at the expense of differentiation (105-fold+-%28% expansion (P<0.01); 20%+-3 neutrophils (P<0.001) taking day 7 as the end-point). In contrast, cells expressing Ras* effector mutants selectively activating Raf (Ras*S35) or PI3K (Ras*C40) did not significantly affect differentiation or proliferative capacity, while Ras*G37 (which selectively activates the RalGEF pathway)

perpetuated proliferation and blocked neutrophil development in a similar manner to Ras* (69-fold+-26 (P<0.05); 25%+-10 neutrophils (P<0.05) at day 7). Neither Ras* nor effector mutants of Ras* significantly affected growth in the presence of IL-3 alone. In order to confirm the predominant role of the RalGEF pathway in blocking neutrophil differentiation, we repeated these experiments using constructs expressing constitutively active downstream effector molecules. As expected, Raf* and PI3K* had no significant effect on differentiation while a constitutively active form of RalGDS (RalGDS-CAAX) was extremely potent in perpetuating proliferation and inhibiting differentiation (53-fold+-12 expansion (P<0.005); 4%+-2 neutrophils (P<0.001) at day 7) demonstrating that this effector alone was sufficient to block neutrophil differentiation. The alternative RalGEF, Rlf-CAAX, was also effective though not to the same degree (40-fold+-4 (P<0.005); 18%+-5 neutrophils (P<0.001)). These data implicate Ral as a likely effector responsible for the anti-differentiation effect of Ras and this is currently the focus of our study. In conclusion, our data demonstrate for the first time, the importance of RalGDS in regulating the differentiation of hematopoietic cells. Given the clinical correlation with JMML, these data also identify potential key therapeutic targets for the treatment of leukemia.

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DIALOG(R)File 5:Biosis Previews(R)

0014379954 BIOSIS NO.: 200300336697
In Vitro Differentiation of AC133-Positive Precursor Cells into Hematopoietic and Endothelial Cells at the Single-Cell Level: Evidence for the Postnatal Hemangioblast.
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ABSTRACT: Recent studies show that human AC133+ cells from granulocyte colony-stimulating (G-CSF)-mobilized peripheral blood comprise stem and progenitor cells not only with the capacity to differentiate into hematopoietic cells, but also to form endothelial cells. To test the hypothesis that this population also contains a common precursor, the hemangioblast, we developed a culture system that allows studies on AC133+ cells at the single-cell level. In the presence of the cytokines vascular endothelial growth factor (VEGF), stem cell growth factor (SCGF), and Flt-3 ligand, AC133+ cells were first expanded and transduced with gibbon ape leukemia virus-pseudotyped FMEV vectors encoding the enhanced freen fluorescent protein (EGFP) marker gene. Single EGFP+ cells were then cocultured with corresponding non-transduced cells. Approximately 8 % of the wells with single-seeded EGFP+ cells yielded more than 30 marked cells after two weeks of culture. Then one half of these cells were grown with G-CSF, while the other was stimulated with SCGF and VEGF. Under the influence of G-CSF, EGFP+ cells differentiated into mature granulocytes as indicated by typical morphology and positive staining for CD13. EGFP+ cells cultured with SCGF and VEGF generated endothelial cells that were identified by expression of VE-Cadherin and binding to Ulex europaeus agglutinin-1. Dual differentiation of EGFP+ cells could be observed in one quarter of clones from single-seeded cells, suggesting that 2 % of EGFP+ cells possessed hemangioblastic potential. AC133+ cells could be expanded for at least %28% days without loosing this dual capacity. Linear amplification-mediated (LAM) PCR analysis suggests that EGFP+ granulocytes as well as endothelial cells might contain same size retroviral integration site amplicons. Direct genomic sequencing is being performed to verify identity at the molecular level.

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DIALOG(R)File 5:Biosis Previews(R)

0014379936 BIOSIS NO.: 200300336679
Clonal Heterogeneity in CD34+38- Human Cord Blood Cells Is Correlated with Gene Expression Pattern and Telomere Length Measured by Flow FISH.
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ABSTRACT: Human hematopoietic stem cells (HSC) are characterized by an extensive proliferation capacity which decreases from fetal liver to cord blood to adult bone marrow. In previous studies, we have demonstrated that the proliferative capacity of individual CD34+CD38- HSC clones is strongly correlated with their initial growth kinetics in vitro. Aim of the current study was to investigate telomere length as a parameter that could be used to characterize the functional hierarchy observed in the human HSC compartment and allow the identification of primitive subpopulations among CD34+CD38- human cord blood cells. Furthermore, differences in gene expression were correlated with growth kinetics of cord blood HSC in vitro. Individual, CD34+CD38- single cells (n = 595) from three different cord blood specimen were sorted directly into 96-well plates containing serum-free medium supplemented with SCF, Flt-3, IL-3, IL-6, G-CSF and TPO. Once sufficient cell numbers were achieved (>200000 cells), telomere length was measured by Flow-FISH and expressed in molecular equivalents of soluble fluorochrome units (kMESF). Of the 595 single sorted CD34+38- cells, 66 colonies yielded more than 100000 cells and were transferred into 24-well plates. Based on the time span it took the individual colony to reach that margin, clones were classified as fast (<39 days), intermediate (39-48 days) and slowly growing clones (>48 days). A total of 27 clones yielded enough cells to allow telomere length analysis by Flow-FISH. Telomere length ranged from 9 to 23 kMESF (median: 14,1 kMESF) and was found to correlate significantly with the growth kinetics of the individual clone (R=0.61; p<0.001). Significantly longer telomere length were found when slowly (n=3)/intermediate (n=4) growing clones were compared to fast (n=20) growing clones (deltaTel = 6.3 kMESF; p<0.0001). In a second set of experiments individual CD34+38- cord blood cells (n=600) from another three different individuals were expanded under the same conditions but individual clones (n=31) were harvested at the level of 10000 cells and frozen down. Global gene expression was analyzed in pooled samples from slowly growing (n=%17%) as compared to fast growing (n=14) HSC clones using oligonucleotide microarrays (HG-U133A, Affymetrix). Analysis of differentially expressed genes revealed 250 genes to be up-regulated and 44 genes to be down-regulated in slowly compared to fast growing HSC clones. Genes identified are involved in lineage determination, protein biosynthesis, cell structure and signal transduction. In summary, individual CD34+ CD38- cells display an extensive functional heterogeneity in growth kinetics. Among highly proliferative clones (<5%), telomere length was

found to be strongly correlated with growth kinetics, i.e. the most slowly growing clones are characterized by the longest telomere length. Furthermore significant differences in gene expression were detected between slowly and fast growing clones. These data provide further evidence for a functional hierarchy in the human HSC compartment and suggest that telomere length measurements and gene expression analysis can be used to identify more primitive subsets among CD34+CD38- cells.

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DIALOG(R)File 5:Biosis Previews(R)

0014379544 BIOSIS NO.: 200300336287
A Novel Conditioning Regimen of Thiotepa, Melphalan, and Cyclophosphamide for Autologous Stem Cell Transplantation (ASCT) in Chemosensitive Multiple Myeloma.
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JOURNAL: Blood 100 (11): pAbstract No. 1687 November 16, 2002 2002
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CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
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LANGUAGE: English

ABSTRACT: Multiple myeloma is an aggressive disease with median survival of 36 months in patients treated with conventional chemotherapy. Recently, dose intensive chemotherapy with autologous stem cell transplantation (ASCT) has been utilized to prolong event free and overall survival (Attal et al NEJM 1996 335:91-97). The current study was designed to evaluate toxicity, DFS, and OS following ASCT using a novel conditioning regimen of thiotepa, melphalan and cyclophosphamide in patients with chemosensitive disease. 42 patients, median age 56 (range 26-70) were enrolled; 81% had stage 3 disease. Patients who failed to achieve a 50% reduction in paraprotein or marrow plasma cells with conventional chemotherapy were ineligible. Stem cells were mobilized with cyclophosphamide (4000 mg/m2) and G-CSF (5 mcg/kg/day). The conditioning regimen consisted of thiotepa (200mg/m2 days -4/-3/-3/-1), melphalan (140 mg/m2 day -3), and cyclophosphamide (1800 mg/m2 day -2/-1) as well as dexamethasone (40 mg/day day -4/-3/-3/-1). Starting on day +5, all patients received G-CSF (5 mcg/kg/day) until neutrophil engraftment. The average time post transplant until ANC>500 was 10.7 days, and until platelets > 20 K without transfusion was 11.3 days. Documented infections occurred in 13/42 patients during their hospitalization and involved various pathogens, including 8 cases of coagulase negative Staphylococcus bacteremia. Day 100 transplant-related mortality was 4.7 %. One patient died at day +30 due to pneumonitis, and one at day +34 due to sepsis. With a median followup of 34 months, %17%/42 (40%) patients have relapsed, and 22/42 (52%) remain in complete remission. Two year DFS and OS following ASCT was 78% and 66%, respectively. The results obtained with this regimen compare favorably with those of previously reported studies, with acceptable toxicity.

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DIALOG(R)File 5:Biosis Previews(R)

0014379196 BIOSIS NO.: 200300335939
Upfront Randomized TAD-HAM vs HAM-HAM Induction, G-CSF Priming vs No G-CSF and Prolonged Maintenance vs Autologous Transplantation in De Novo AML, Secondary AML and High-Risk MDS and Their Subgroups According to Cytogenetics and LDH: Interim Analysis.
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JOURNAL: Blood 100 (11): pAbstract No. 1339 November 16, 2002 2002
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LANGUAGE: English

ABSTRACT: The benefit from major treatment alternatives for AML patients in different prognostic groups has been studied by retrospective, explorative analyses with conflicting results (Lancet 351:700, 1998; Cancer Res. 58:4173, 1998; Blood 93:4116, 1999; Blood 96:4075, 2000). More conclusive answers, however, may not be given by the recent risk factor guided strategies. As a strictly prospective approach to subgroup specific treatment we therefore designed a multicenter study, where all patients are randomized upfront in a one-step procedure for several treatment decisions, balancing each randomization against the others: (1) one vs. two induction courses with high-dose AraC (TAD-HAM vs HAM-HAM); (2) G-CSF before and during chemotherapy vs. no G-CSF; (3) prolonged maintenance vs. autologous transplantation. Each randomization is also balanced for the following AML subgroups: (1) de novo AML vs. AML secondary to MDS or to cytotoxic treatment vs. high-risk MDS, (2) favorable vs. unfavorable vs. other cytogenetics, (3) high vs. low serum LDH, (4) age 60+ vs. <60 y. Younger patients in all subgroups are considered randomized to allogeneic transplantation if a histocompatible family donor is available. Starting in June 1999 1137 patients 16-81 (median 59) y of age entered the study. 49 % of patients were 60 y or older, 78 % presented with de novo AML, 16 % with sAML, and 6 % with high-risk MDS. Cytogenetics were available in more than 95 % of cases with 9 % favorable, 24 % unfavorable, and 67 % others, LDH > 700 U/l was found in %28% % of the patients. The overall CR rate is 58 % with 62 % in de novo AML, 50 % in MDS and 41 % in secondary AML (p = .001), 63 % in younger and 53 % in older patients (p = .009), 66 % in favorable and 44 % in unfavorable cytogenetics (p = .003), 59 % in low LDH and 56 % in high LDH (n.s.). The median overall survival is 11 months with 12 in de novo AML, 8 in MDS and 6 in sAML (p = 0.001), 14 in younger and 8 in older patients (p < 0.001), 25 in favorable and 6 in unfavorable cytogenetics (p < 0.001), 12 in low and 9 in high LDH (p = .004). The median RFS is 12 months with 13 in de novo AML, 9 in MDS, and 12 in secondary AML (n.s.), %17% in younger and 9 in older patients (p < 0.001), 24 in favorable and 6 in unfavorable cytogenetics (p < 0.001), and 15 in low and 9 in high LDH (p < 0.001). EFS from treatment start and RFS as primary endpoints are not different between treatment arms, so far. Like prognostic groups and treatment assignments also the delivery of treatment regimens prove to be balanced between randomized arms thus demonstrating the one step upfront randomization as a successful approach. By the design and high accrual rate the study will provide for the first time reliable, non-selected, intent-to-treat-based information about subgroup-specific differential treatment effects in AML.

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DIALOG(R)File 5:Biosis Previews(R)

0014379191 BIOSIS NO.: 200300335934
Efficacy and Toxicity of the FLAG/Daunoxome(R) Association in Children with Relapsed or Resistant Acute Myeloid Leukemia (AML).
AUTHOR: Rizzari Carmelo (Reprint); Micalizzi Concetta (Reprint); Locatelli Franco (Reprint); Maffeis Barbara (Reprint); Daldossi Silvia (Reprint); Ladogana Saverio (Reprint); Casale Fiorina (Reprint); Fagioli Franca (Reprint); Lippi Alma (Reprint); Colombini Antonella (Reprint); Pession Andrea (Reprint)
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JOURNAL: Blood 100 (11): pAbstract No. 1334 November 16, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 44th Annual Meeting of the American Society of Hematology Philadelphia, PA, USA December 06-10, 2002; 20021206
SPONSOR: American Society of Hematology
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: The prognosis of patients with resistant or relapsed AML is dismal despite the use of intensive chemotherapy schedules and bone marrow transplantation (BMT). Preliminary data on the efficacy of the FLAG schedule with or without anthracyclines in these patients are promising. Aim of the study: To evaluate retrospectively the toxicity/efficacy in children with resistant or relapsed AML treated with the association FLAG/Daunoxome(R). Patients and methods: Nineteen children (12 M / 7 F) with resistant (n=4) or relapsed (n=15, 4 after chemotherapy and 11 after BMT (8 autologous and 3 allogeneic)) AML underwent a chemotherapy schedule consisting of FLAG (Fludarabine 30 mg/mq/die i.v. and ARA-C 2 gr/mq/die i.v. dd 1-5, G-CSF 200 mcg/mq/die dd 0-5 and from d +15 until neutrophils recovery) + Dunoxome(R) (60 mg/mq/die i.v. dd 1, 3, 5) in the period 1.1.01-1. 29.02. Results and follow-up were evaluated at the cut-off date of 2.%28%.2002. Results: Median age was 4.7 yrs (range 0.2-13.7 yrs) at first diagnosis and 8.7 yrs (range 0.8-14.6 yrs) when the FLAG/Daunoxome(R) cycle was administered. In the 15 relapsed patients the median duration of the 1st CR was 1.07 yrs (range 0.3 - 4.7 yrs). Efficacy: CR was obtained in 14/19 (73%) pts (13/15 relapses and 1/4 resistant). 4/4 pts relapsed after a chemotherapy protocol and 9/11 pts relapsing after BMT obtained a new CR. Median time of neutrophils (gtoreq500/mmc) and platelets (gtoreq50000/mmc) recovery was 22 (range 7-51) and 25 (range 7-65) dd respectively. Toxicity (pts): Grade 3 mucositis (1), sepsis (1), fungal pneumonia (1). Neither cardiotoxicity nor toxic deaths were observed. Four of the 5 pts who did not achieve CR died and 1 is alive with disease. Of the 14 pts who achieved CR: 9 underwent BMT (1 autologous and 8 allogeneic; of these 7 are still alive and in continuous CR); 1 was lost to follow-up; 1 relapsed; 1 died while in CR; 2 are alive and in CR but with a very short follow up. Conclusions: In this experience the use of FLAG/Daunoxome(R) allowed the CR attainment in a relatively large proportion of children with relapsed AML without relevant toxicity. Children with resistant AML had less favourable results.

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0014379160 BIOSIS NO.: 200300335903
Documentation of Problems with Use of Historical Controls/Single Arm Phase II Trials in Newly-Diagnosed AML.
AUTHOR: Estey Elihu H (Reprint); Shen Yu (Reprint); Thall Peter F (Reprint) ; Cortes Jorge E (Reprint); Thomas Deborah (Reprint); Faderl Stefan H (Reprint); Verstovsek Srdan (Reprint); Beran Miloslav (Reprint); Keating Michael J (Reprint); O'Brien Susan (Reprint); Kantarjian Hagop M (Reprint); Giles Francis J (Reprint)
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Phase II trials are often viewed as means to establish activity of a new agent (E). Although the majority of such trials are single-arm, they inherently involve a comparison between E and a standard treatment S, as given in a prior trial. Indeed, the decision to proceed to phase III is based, at least informally, on the results of the comparison. The comparison assumes however that observed differences between E and S are entirely due to (1) differences in therapeutic efficacy, (2) differences between E and S in the distribution of known covariates (age, cytogenetics etc), or (3) random variation. We tested this assumption by comparing covariate-adjusted outcomes following administration of the same regimen (idarubicin 12 mg/m2 daily X 3, ara-C 1.5 g/m2 daily X4 CI) given in separate trials in newly-diagnosed AML. In each trial both the induction and post-remission regimens were identical, patients over age 50 were treated in laminar airflow rooms, and anti-bacterial/ anti-fungal prophylaxis (although with different agents) was used. Results were inferior in trial 2: The inferiority did not arise as a result of the excess of older patients or patients with poor prognosis cytogenetics in trial 2 since multivariate regression indicated that, after accounting for these and other well-known covariates, the risk of death in this later trial was 1.9-fold the risk in the earlier trial (p=.049). The inferior survival in trial 2 reflected both a shorter time to failure of initial treatment and shorter DFS once in initial CR; the covariate-adjusted risk of relapse from, or death in, initial CR was 1.9-fold higher in the later trial (p=.09). These differences between the same treatment given in separate trials, which appear considerably more than expected via the play of chance, are referred to as "trial effects" (TE). We have also observed such TEs in separate trials in patients age >64 of (1) fludarabine, ara-C, idarubicin, + g-csf (FLAG - ida) as given in 1993-1995 (24 patients) and again in 1995-1997(34 patients) and (2) FLAG - ida + ATRA as given in 1995 (%17% patients) and again in 1995-1997 (44 patients). In particular, the covariate-adjusted probabilities that the risk of death was greater in the earlier trial were 89% (FLAG-ida) and 87% (FLAG - ida + ATRA), with these probabilities again more than expected from random variation. The documentation of such TEs highlight the difficulties attendant on the use of historical data/single arm phase II trials to assess the efficacy of new treatments in AML or of comparing trials of the same treatment as conducted at different institutions.

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0014378776 BIOSIS NO.: 200300335519
Complete Inhibition of Neutrophil Elastase Fails To Correct the In Vitro Phenotype of Severe Congenital Neutropenia.
AUTHOR: Ancliff Philip J (Reprint); Gale Rosemary E (Reprint); Somerville Tim C (Reprint); Kwaja Asim (Reprint); Liesner Ri (Reprint); Hann Ian M (Reprint); Linch David C (Reprint)
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JOURNAL: Blood 100 (11): pAbstract No. 919 November 16, 2002 2002
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ABSTRACT: Severe congenital neutropenia (SCN) is characterised by profound neutropenia, recurrent bacterial infections and maturation arrest at the

myelocyte stage. Genetic data supports a causal role for heterozygous mutations in the ELA2 gene encoding neutrophil elastase (NE). Studies in a phenotypically normal chimera bearing a NE mutation suggest that aberrant elastase has a direct effect on the cell in which it is produced. However, a convincing pathogenetic mechanism remains elusive. Putative mechanisms include direct toxicity of mutant NE that cannot be properly packaged and metabolism of an atypical substrate within the developing myeloid cell. We therefore postulated that complete intracellular inhibition of NE might improve the SCN phenotype, as mice expressing no NE have normal neutrophil counts. To explore this hypothesis, we developed an in vitro model of SCN in which CD34+ cells are cultured in IMDM / 20% FCS with SCF (20ng/ml), IL-3 (20ng/ml) and G-CSF (100ng/ml) for 14 days. In this system >90% of cells at the end of culture from controls are metamyelocytes or neutrophils, whereas in 6 cases of SCN the total number of cells generated in culture was reduced and there was a marked decrease in the metamyelocyte/neutrophil fraction. The effects of 3 neutrophil elastase inhibitors (GW311616A (gift of GlaxoSmithKline, UK), ZD0892 (gift of AstraZeneca, Sweden) and ZR-M200355 (AstraZeneca)) on CD34+ cells from 2 controls and 2 SCN children were examined. One patient with SCN had a heterozygous G2202A (Gly56Glu) NE mutation and the other had presumed autosomal recessive SCN (we postulated that such disease could be due to deficiency of a physiological elastase inhibitor). Persistence of inhibitory activity throughout the culture period was demonstrated for all 3 compounds by incubating diluted culture media with human NE and assay with the fluorescent EnzChek(R) Elastase AssayKit, (Molecular Probes, OR). "Mature" myeloid cells were lysed at the end of the culture period and these lysates assayed for NE activity using the same fluorescent substrate. Complete inhibition of intracellular NE could only be demonstrated for GW311616A, at concentrations as low as 100nM. However, even at a concentration of 1muM of GW311616A there was no increase in the expansion of the elastase mutant patient's cells, 39-fold compared with 43-fold (patient) and 122-fold (mean of the 2 controls) without the addition of the inhibitor. Similarly, the proportion of metamyelocytes and neutrophils at day 14 did not increase, %28%% compared to 37% in the absence of inhibitor and over 90% in the controls. Similar results were obtained for the autosomal recessive patient, 53-fold versus 32-fold expansion and 29% versus 34% metamyelocytes and neutrophils for the control and 1muM concentration of GW311616A respectively. This data suggests that the mechanism of neutropenia in SCN is not due to the metabolism of an atypical substrate. It also argues against the role of deficiency of elastase inhibitors in at least some autosomal recessive SCN. Furthermore, we have directly sequenced the monocyte/neutrophil elastase inhibitor (the most potent intra-cellular elastase inhibitor) in 4 families (2 autosomal dominant and 2 recessive) without ELA2 mutations and only identified 8 apparently non-pathological intronic polymorphisms.

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DIALOG(R)File 5:Biosis Previews(R)

0014303403 BIOSIS NO.: 200300262047
Analysis of PBPC cell yields during large-volume leukapheresis of subjects with a poor mobilization response to filgrastim.
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JOURNAL: Transfusion (Bethesda) 43 (4): p495-501 April 2003 2003
MEDIUM: print
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: BACKGROUND: The circulating CD34 count is a reliable predictor of peripheral blood progenitor cell (PBPC) yields in subjects with a vigorous mobilization response to G-CSF, however, the value of this parameter in poor mobilizers is uncharacterized. STUDY DESIGN AND METHODS: Consecutive PBPC procedures (n = 81) with preapheresis CD34 counts less than 20 per muL (poor mobilizers) were compared with an equal number of good mobilizers (preapheresis CD34 counts gtoreq20/muL). G-CSF was administered at standard doses (10 mug/kg/day). RESULTS: CD34 yields correlated strongly with preapheresis CD34 counts in both good and poor mobilizers and were higher in allogeneic than autologous donors. For a standard 75-kg recipient, a CD34 cell dose of greater than 2 X 106 per kg was never achieved in less than two 15-L procedures if the preapheresis CD34 count was less than 8 per muL. Preapheresis WBC and MNC counts were lower in poor than in good mobilizers (%28%.4 vs. 43.0 and 3.25 vs. 5.01 X 103/muL, respectively, p < 0.0001). Total WBC counts correlated more strongly with preapheresis CD34 counts, total CD34 yields, and CD34 yields per L processed in good mobilizers (R = 0.50, R = 0.44, and R = 0.42, respectively) than in poor mobilizers (R = 0.22, R = 0.02, and R = 0.01, respectively), whereas total MNC counts correlated more strongly with these parameters in poor (R = 0.38, R = 0.23, and R = 0.27, respectively) than in good mobilizers (R = 0.04, R = 0.13, and R = 0.16, respectively). CONCLUSION: CD34 cell yields correlate strongly with preapheresis CD34 counts. Based on this analysis, a CD34 count greater than or equal to 8 per muL is the threshold for performing PBPC collections in our institution.

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DIALOG(R)File 5:Biosis Previews(R)

0014289379 BIOSIS NO.: 200300248098
Salvage treatment of metastatic breast cancer with docetaxel and carboplatin. A multicenter phase II trial.
AUTHOR: Mavroudis D (Reprint); Alexopoulos A; Malamos N; Ardavanis A; Kandylis C; Stavrinidis E; Kouroussis Ch; Agelaki S; Androulakis N; Bozionelou V; Georgoulias V
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JOURNAL: Oncology (Basel) 64 (3): p207-212 April 2003 2003
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ABSTRACT: Objectives: To evaluate the efficacy and safety of docetaxel in combination with carboplatin as salvage treatment in women with metastatic breast cancer (MBC). Patients and Methods: Chemotherapy-pretreated women with MBC were treated with docetaxel 75 mg/m2 as 1-hour i.v. infusion followed by carboplatin AUC 6 mg/mlcntdotmin, using the Calvert's formula, as 30-min i.v. infusion. Cycles were repeated on an outpatient basis every 3 weeks. Results: Thirty-six patients received a total of 210 chemotherapy cycles (median 6 cycles/patient). All but one patient had previously received anthracyclines for the treatment of metastatic disease and half of the patients had failed to respond to front-line treatment. Twenty-eight (78%) patients had visceral disease. On an intention-to-treat analysis there were three (8%) complete and 19 (53%) partial responses for an overall response rate of 61% (95% CI: 45.2-77.0%). The response rate was 44% (2 CRs, 6 PRs) among 18 patients who had progressive or stable disease as best response to front-line treatment. The median duration of response was 8 months, the median time to tumor progression 10 months, and the probability of 1-year survival 66%. Grade 3-4 neutropenia was the main hematologic toxicity occurring in 16 (45%) patients or 36 (%17%%) cycles. Seven (19%) patients developed 8 (4%) febrile neutropenic episodes. Grade 3 thrombocytopenia occurred in 4 (11%) patients or 6 (3%) cycles. Non-hematologic toxicity was generally mild. G-CSF was used in 19 (53%) patients or 134 (64%) cycles. There was one sudden death possibly related to the treatment. Conclusion: The docetaxel-carboplatin combination is an active outpatient salvage regimen for the treatment of

women with MBC relapsing or not responding to anthracycline-based front-line therapy.

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DIALOG(R)File 5:Biosis Previews(R)

0014059442 BIOSIS NO.: 200300018161
Administration of low-dose interleukin-2 plus G-CSF/EPO early after autologous PBSC transplantation: Effects on immune recovery and NK activity in a prospective study in women with breast and ovarian cancer.
AUTHOR: Perillo A (Reprint); Pierelli L; Battaglia A; Salerno M G; Rutella S; Cortesi E; Fattorossi A; De Rosa L; Ferrau F; Lalle M; Leone G; Mancuso S; Scambia G
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JOURNAL: Bone Marrow Transplantation 30 (9): p571-578 November 1, 2002 2002
MEDIUM: print
ISSN: 0268-3369 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
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ABSTRACT: This study evaluated the effects of low-dose IL-2 plus G-CSF/EPO on post-PBSC transplantation (PBSCT) immune-hematopoietic reconstitution and NK activity in patients with breast (BrCa) and ovarian cancer (OvCa). To this end, two consecutive series of patients were prospectively assigned to distinct post-PBSCT cytokine regimens (from day +1 to day +12) which consisted of G-CSF (5 mug/kg/day) plus EPO (150 IU/kg/every other day) in %17% patients (13 BrCa and 4 OvCa) or G-CSF/EPO plus IL-2 (2X105 IU/m2/day) in 15 patients (10 BrCa and 5 OvCa). Hematopoietic recovery and post-transplantation clinical courses were comparable in G-CSF/EPO- and in G-CSF/EPO plus IL-2-treated patients, without significant side-effects attributable to IL-2 administration. In the early and late post-transplant period a significantly higher PMN count was observed in G-CSF/EPO plus IL-2-treated patients (P=0.034 and P=0.040 on day +20 and +100, respectively). No significant differences were found between the two groups of patients in the kinetics of most lymphocyte subsets except naive CD45RA+ T cells which had a delayed recovery in G-CSF/EPO plus IL-2 patients (P=0.021 on day +100). No significant difference was observed between NK activity in the two different groups, albeit a significantly higher NK count was observed in G-CSF/EPO plus IL-2 series on day +20 (P=0.020). These results demonstrate that low-dose IL-2 can be safely administered in combination with G-CSF/EPO early after PBSCT and that it exerts favorable effects on post-PBSCT myeloid reconstitution, but not on immune recovery.

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DIALOG(R)File 5:Biosis Previews(R)

0014055786 BIOSIS NO.: 200300014505
Efficacy and safety of G-CSF mobilized granulocyte transfusions in four neutropenic children with sepsis and invasive fungal infection.
AUTHOR: Grigull L (Reprint); Schrauder A; Schmitt-Thomssen A; Sykora K; Welte K
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JOURNAL: Infection 30 (5): p267-271 October 2002 2002
MEDIUM: print
ISSN: 0300-8126
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Bacterial and fungal infections are serious complications of cancer therapy. Especially during longstanding neutropenia, patients are at risk for life-threatening infections. The aim of this study was to assess the effect and safety of G-CSF mobilized granulocyte transfusions (GTX) in four neutropenic pediatric patients with sepsis. Patients and Methods: The patients were between 4.6-%17%.5 years old and their diagnoses included very severe aplastic anemia, non-Hodgkin's lymphoma (NHL) and acute myeloid Leukemia. Before GTX, all patients had fever despite antibiotic and antimycotic therapy, neutropenia (absolute neutrophil count ANC<500/mul), increasing C-reactive protein (CRP) values, hypotension requiring dopamine infusion and three patients needed supplemental oxygen. The granulocyte donors received G-CSF (NeupogenTM, 5 mug/kg body weight) 12 h prior to granulocyte apheresis. Results: In total, 40 GTX were performed (range 2-%28% per patient). The mean increase of the granulocyte count 1 h after GTX was 1,310/mul (range 200-2,950/mul). Within the period of GTX the CRP values decreased in all patients. During or 24 h after the Last GTX, the hypotension resolved and supplemental oxygen was stopped. One GTX was discontinued because of oxygen desaturation. Conclusion: GTX were a safe therapeutic measure with beneficial effects on serious infections in neutropenic children.

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DIALOG(R)File 5:Biosis Previews(R)

0011182382 BIOSIS NO.: 199799816442
High-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with multiple myeloma and renal insufficiency
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JOURNAL: Bone Marrow Transplantation 20 (8): p653-656 1997 1997
ISSN: 0268-3369
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Six patients with multiple myeloma and chronic renal insufficiency (serum creatinine gt 3.0 mg/dl), including four on dialysis, received high-dose busulfan and cyclophosphamide (BUCY) followed by autologous peripheral stem cell transplantation. Peripheral blood stem cells were collected after printing with cyclophosphamide, etoposide and G-CSF. Patterns of engraftment and toxicities were not apparently different from those seen in myeloma patients with normal renal function. There was one toxicity-related death, resulting from a massive spontaneous subdural hematoma. One patient died of disease progression 6 months after transplant, while the remaining four patients are alive and free of myeloma progression 6 to 39 months after high-dose therapy. Two of these patients have remained in complete remission for %28% and 39 months. Our experience suggests that high-dose therapy with BUCY and autologous peripheral blood stem cell rescue is feasible in patients with multiple myeloma and renal failure.

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DIALOG(R)File 5:Biosis Previews(R)

0011114184 BIOSIS NO.: 199799748244
Cell cycle analysis and synchronization of pluripotent hematopoietic progenitor stem cell
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JOURNAL: Blood 90 (6): p2293-2299 1997 1997
ISSN: 0006-4971
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hematopoietic stem cells purified from mouse bone marrow are quiescent with less than 2% of Lin- Hoechst-low/Rhodamine-low (Lin-Ho-low/Rho-low) and 10% to 15% of Lin-/Sca+ cells in S phase. These cells enter proliferative cycle and progress through G-1 and into S phase in the presence of cytokines and 5% heat-inactivated fetal calf serum (HI-FCS). Cytokine-stimulated Lin- Ho-low/Rho-low cells took 36 to 40 hours to complete first division and only 12 hours to complete each of 5 subsequent divisions. These cells require 16 to 18 hours to transit through G-0/G-1 period and %28% to 30 hours to enter into mid-S phase during the first cycle. Up to 56% of Lin- Rho-low/Ho-low- cells are high-proliferative potential (7 factor-responsive) colony-forming cells (HPP-CFC). At isolation, HPP-CFC are quiescent, but after %28% to 30 hours of culture, greater than 60% are in S phase. Isoleucine-deprivation of Lin-Ho-low/Rho-low cells in S phase of first cycle reversibly blocked them from entering into second cycle. After the release from isoleucine-block, these cells exhibited a G-1 period of less than 2 hours and entered into mid-S phase by 12 hours. Thus, the duration of G-1 phase of the cells in second cycle is 4 to 5 times shorter than that observed in their first cycle. Similar cell cycle kinetics are observed with Lin-/Sca+ population of bone marrow cells. Stem cell factor (SCF) alone, in the presence of HI-FCS, is as effective as a cocktail of 2 to 7 cytokines in inducing quiescent Lin-/Sca+ cells to enter into proliferative cycle. Aphidicolin treatment reversibly blocked cytokine-stimulated Lin-/Sca+ cells at G-i/S boundary, allowing their tight synchrony as they progress through first S phase and enter into second G-1. For these cells also, SCF alone is sufficient for their progression through S phase. These studies indicate a very short G-1 phase for stem cells induced to proliferate and offer experimental approaches to synchronize murine hematopoietic stem cells.

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DIALOG(R)File 5:Biosis Previews(R)

0011091225 BIOSIS NO.: 199799725285
Bone marrow repopulation by human marrow stem cells following long-term expansion culture on a porcine endothelial cell line
AUTHOR: Brandt J (Reprint); Galy A; Luens K; Travis M; Young J; Tong J; Davis T; Lee K; Chen B; Tushinski R; Hoffman R
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JOURNAL: Experimental Hematology (Charlottesville) 25 (8): p739 1997 1997
CONFERENCE/MEETING: 26th Annual Meeting of the International Society for Experimental Hematology Cannes, France August 24-28, 1997; 19970824
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DIALOG(R)File 5:Biosis Previews(R)

0010956428 BIOSIS NO.: 199799590488
Blood concentrations of G-CSF and myelopoiesis in patients undergoing aortocoronary bypass surgery
AUTHOR: Usui A (Reprint); Kawamura M; Hibi M; Yoshida K; Murakami F; Tomita Y; Ooshima H; Murase M
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JOURNAL: Annals of Hematology 74 (4): p169-173 1997 1997
ISSN: 0939-5555
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The pattern of changes in leukocyte counts and the blood concentration of G-CSF were observed in 15 patients undergoing aortocoronary bypass surgery. Myelopoietic function was assessed by examining the myelogram and performing flow cytometry to identify human leukocyte differentiation antigens on bone marrow aspirates obtained from the sternum when opening and closing the sternotomy. The blood concentration of G-CSF increased gradually after removal of the aortic cross clamp and peaked on the first postoperative day (232 +- 98 ngml). The white blood cell count also increased during the operation and peaked on the second postoperative day, demonstrating a threefold increase (15800 +- 2700). Granulocytes represented most of the increase, while lymphocytes and monocytes showed no significant changes. The myelogram showed that the percentages of myeloblasts, promyelocytes, and metamyelocytes did not change; however, the percentage of myelocytes increased significantly during surgery (14.0 +- 2.5% vs. %17%.3 +- 3.5%, p lt 0.05). The number of mature myelocytes (LFA-1-beta and Leu-15 positive) decreased significantly (p lt 0.01 and p lt 0.05) during surgery. With the two-color method, the ratio of immature myelocytes (MCS-2 negative and Leu-15 negative) increased significantly (p lt 0.01). The ratio of myeloblasts (Leu-11 and HLA-DR positive) and the ratio of stem cells (CD 34 and MY-9 positive) did not increase significantly during the operation. G-CSF concentrations increase substantially during aortocoronary bypass surgery and may be responsible for the rise in granulocyte and total leukocyte counts, as well as for the increase in immature myelocytes seen on bone marrow examination.

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DIALOG(R)File 5:Biosis Previews(R)

0010871875 BIOSIS NO.: 199799505935
Blood progenitor cell (BPC) mobilization studied in multiple myeloma, solid tumor and non-Hodgkin's lymphoma patients after combination chemotherapy and G-CSF
AUTHOR: Engelhardt M (Reprint); Winkler J; Waller C; Lange W; Mertelsmann R ; Henschler R
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JOURNAL: Bone Marrow Transplantation 19 (6): p529-537 1997 1997
ISSN: 0268-3369
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: For blood progenitor cell (BPC) mobilization, standard-dose VIP chemotherapy consisting of etoposide, ifosfamide and cisplatin has previously shown effective tumor reduction in solid tumor patients and sufficient progenitor cell mobilization for autologous blood cell transplantation. Mobilization chemotherapy regimens in multiple myeloma (MM) predominantly consist of melphalan or cyclophosphamide that induce marked cytopenia and considerable variability of progenitor cell collection. We studied whether in MM (n = 13), BPCs were efficiently and reproducibly mobilized with etoposide (500 mg/m-2) and ifosfamide (1500 mg/ml), followed by daily s.c. G-CSF (5 mu-g/kg). In parallel, patients with solid tumors or non-Hodgkin's lymphomas (n = %28%) treated with etoposide (500 mg/m-2), ifosfamide (1500 mg/ml) and cisplatin (150 mg/ml) and identical dosing of G-CSF were analyzed. Before chemotherapy (day 0), on day 7 after chemotherapy and on days of leukapheresis (day 9-14), leukocyte numbers, mononuclear cells (MNCs), CD34+ cells and coexpression of lineage markers were analyzed. Median blood leukocyte numbers were 28100/mu-l (range, 19600-40400) on day 10 in myeloma patients and progressively declined over the next 4 days. In contrast, in solid tumor and lymphoma patients leukocyte numbers constantly increased from a median of 12400/mu-l (range, 6000-22000) to 30000/mu-l (range, 16300-63300) between day 10 and day 13 after chemotherapy. Similar to leukocyte counts, median MNC numbers decreased in myeloma patients with

successive leukaphereses, but steadily increased in solid tumor and lymphoma patients over the same period. CD34+ cell numbers in the blood peaked between day 9 and 11 (median: 40/mu-l) in myeloma patients and then declined. In the solid tumor and lymphoma group, median CD34+ counts in the blood peaked on day 12 after mobilization chemotherapy (median: 100/mu-l). The median CD34+ yield per leukapheresis in the myeloma group was 2.2 times 10-6/kg (range, 1.5-4.7) on day 10, and fell steadily to 0.95 times 10-6/kg on day 12, whereas in solid tumor/NHL patients median CD34+ cell yields remained between 3.5 and 3.7 times 10-6/kg from day 10 to day 12 after mobilization chemotherapy (P lt 0.001). To obtain sufficient cell numbers for engraftment a median of 2 (range, 1-3) mobilization chemotherapy cycles were needed in MM compared to 1 (range, 1-10) in solid tumor or lymphoma patients, with a median of 5 (range, 2-8) leukaphereses in MM compared to 1 (range, 1-10) (P lt 0.05). Taken together, we found that for patients with MM, VP16 and ifosfamide efficiently and predictably mobilizes progenitor cells into the PB with gtoreq 3 times 10-6/kg CD34+ cells collected after one to two mobilization chemotherapy cycles.

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DIALOG(R)File 5:Biosis Previews(R)

0010771283 BIOSIS NO.: 199799405343
Successful engraftment after primary graft failure in aplastic anemia using G-CSF mobilized peripheral stem cell transfusions
AUTHOR: Redei I (Reprint); Waller E K; Holland H K; Devine S M; Wingard J R
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JOURNAL: Bone Marrow Transplantation 19 (2): p175-177 1997 1997
ISSN: 0268-3369
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A 19-year-old male underwent allogeneic BMT for severe aplastic anaemia (SAA) from his HLA- and blood group-identical sister. He was conditioned with cyclophosphamide (CY) and single fraction total lymphoid irradiation (TLI). GVHD prophylaxis consisted of FK506 and a short course of methotrexate. The patient failed to achieve durable trilineage hematopoietic engraftment. There was no significant myeloid response to GM-CSF or G-CSF. Evaluation of FACS-sorted peripheral T cells from the patient by fluorescence in situ hybridization (FISH) revealed mixed chimerism (44% host origin). Fifty-three days after the first BMT, he was treated with G-CSF primed, unmanipulated PBSC transfusions (5.%28% times 10-8/kg mononuclear, 4.%28% times 10-6/kg CD34+, 292.51 times 10-6/kg CD3+ cells) from his original donor without reconditioning. FK506 was continued at the same dose. Neutrophil recovery to 0.5 times 10-9/l and platelet engraftment to 20 times 10-9/l was achieved 11 and 27 days following the first dose of allogeneic PBSC transfusion, respectively. On day 23 a repeat FISH on the patient's sorted peripheral T lymphocytes revealed 91% donor origin T cells. The patient is currently well with a stable engraftment 6 months following allogeneic PBSC transfusion, with no signs of acute of chronic GVHD.

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DIALOG(R)File 5:Biosis Previews(R)

0010771277 BIOSIS NO.: 199799405337
Effect of the in vivo priming regimen for peripheral blood stem cells (PBSC) mobilization on in vitro generation of cytotoxic effectors by IL-2 activation of PBSC in a murine model
AUTHOR: Verma U N; Yankelevich B; Hodgson J; Mazumder A (Reprint)
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JOURNAL: Bone Marrow Transplantation 19 (3): p265-273 1997 1997
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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Priming of patients with different PBSC mobilizing regimens leads to an increase by several fold in circulating hematopoietic progenitors in peripheral blood. However, the effect of these mobilizing regimens on lymphoid cells contained within the harvested PBSC population is not well understood. We have studied the effect of CY and/or G-CSF +- IL-2 containing regimens on lymphoid cells, and their capacity to give rise to cytotoxic effectors on subsequent in vitro IL-2 activation in a murine model of PBSC mobilization. C57Bl/6 mice were given CY 100 or 200 mg/kg on day 0 followed 48 h later by G-CSF 125 mu-g/kg twice a day and/or IL-2 60 000 IU twice a day in different schedules. Mice were sacrificed on day 4, 6, 8 and 10 following CY and the number of hematopoietic progenitors mobilized to the spleens of these mice was assessed by CFC assay and cytotoxicity was evaluated by 4 h 51Cr release assay against both NK-sensitive (Yak-1), and NK-resistant (B16, C1498) cell lines after 24 h in vitro IL-2 activation in the presence of 6000 IU/ml of IL-2. Peak numbers of CFC in the splenic PBSC population were seen on day 6 following CY. Administration of CY 200 mg/kg + GCSF, the most potent regimen for CFC mobilization, led to a marked decrease in proportion of CD3+ cells in day 6 PBSC as compared to controls (%17%.7% Ps 3.9%) and was associated with a significant decrease in generation of cytotoxic cells after IL-2 activation. Combining IL-2 to CY + G-CSF prevented the marked loss in cytotoxicity associated with this regimen without any decrease in number of CFC mobilized. When IL-2 was combined with CY without G-CSF, the number of CFC mobilized was comparable to that seen with CY + G-CSF and these CY + IL-2 mobilized PBSC generated potent cytotoxic effectors after in vitro IL-2 activation. Thus our results indicate that combining IL-2 with a PBSC mobilizing regimen can avert a decrease in the cytotoxic potential of mobilized cells without compromising the number of hematopoietic progenitors.

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DIALOG(R)File 5:Biosis Previews(R)

0010740279 BIOSIS NO.: 199799374339
Effects of short-term in vivo administration of G-CSF on bone marrow prior to harvesting
AUTHOR: Dicke Karel A (Reprint); Hood Deborah L; Arneson Mark; Fulbright Lorene; Distefano Alfred; Firstenberg Barry; Adams John; Blumenschein George R
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JOURNAL: Experimental Hematology (Charlottesville) 25 (1): p34-38 1997 1997
ISSN: 0301-472X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The brief administration of G-CSF to previously treated solid tumor patients has a positive impact on the overall cellularity and progenitor cell content of harvested bone marrow. Fifty-seven patients, fully recovered from therapy and growth factor support, had approximately 500 mL of steady-state marrow harvested as outpatients under local anesthesia. Each patient then received 5 mu-g/kg of G-CSF every 12 hours subcutaneously for either 24 hours (21 patients), 36 hours (20 patients), or 48 hours (16 patients) just before harvesting 500 mL of activated bone marrow. Bone marrow cellularity (times 10-6/mL) increased from a steady-state mean of 10.7 (+- 0.9) to 25.7 (+- 2.8) after 24 hours, 9.3 (+- 0.7) to 29 (+- 2.5) after 36 hours, and 9.6 (+- 0.7) to %28%.4 (+- 2.5) after 48 hours. Although the percentage of CD34+ cells did not significantly change in stimulated marrow, the total number of CD34+ cells (times 10-6) collected increased from 34 (+- 6.3) to 52 (+- 6.6) after two injections, %28% (+- 3.6) to 65 (+- 8.5) after three injections, and %28% (+- 5.4) to 75 (+- 18) after four injections of G-CSF. Further phenotyping demonstrated significant increases in

CD34+HLA-DR+ cells with all three schedules relative to steady-state marrow. There were no changes in the total number of CD34+HLA-DR- cells after two and four shots; however, this population increased from 10 times 10-6 in steady-state marrow to 23 times 10-6 (p = 0.012) after three injections. Analysis of peripheral blood indicated a statistically significant increase in the circulating white count, but more interestingly, there were significant increases in the number of CD34+ cells times 10-4/mL, suggesting the onset of mobilization. Steady-state blood contained a mean of 0.86 times 10-4/mL CD34+ cells, which increased to 4.37 times 10-4/mL, 7.43 times 10-4/mL, and 8.62 times 10-4/mL after two, three, and four injections, respectively-levels of CD34+ cells that are comparable to steady-state marrow. Reinfusion of a median of 1.6 times 10-6 activated CD34+ cells/kg resulted in the recovery of gt 100/mm-3 neutrophils and gt 20,000 platelets by days 9 and 19, respectively, which was faster than our previous patients who received steady-state marrow, and comparable to our patients who received mobilized peripheral stem cells.

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DIALOG(R)File 5:Biosis Previews(R)

0010719744 BIOSIS NO.: 199799353804
Transplantation with CD34+ autologous peripheral blood progenitor cell (PBPC) mobilized with G-CSF alone in high-risk multiple myeloma (MM): One-center study in %17% patients (PTS)
AUTHOR: Mahe B; Moreau P; Le Tortorec S; Bulabois C; Rapp M I; Cassidanius A; Bercegaey S; Dehaut F; Milpied N; Harousseau I L
AUTHOR ADDRESS: Serv. Hematologie, Nantes, France**France
JOURNAL: Blood 88 (10 SUPPL. 1 PART 1-2): p406A 1996 1996
CONFERENCE/MEETING: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996; 19961206
ISSN: 0006-4971
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DIALOG(R)File 5:Biosis Previews(R)

0010679290 BIOSIS NO.: 199799313350
Mobilization of peripheral stem cells with intensive chemotherapy (ICE regimen) and G-CSF in chronic myeloid leukemia
AUTHOR: Boque C (Reprint); Petit J; Sarra J; Cancelas J A; Munoz J; Espanol J I; De La Banda E; Aventin A; Berlanga J; Ferra C; Amill B; Torrico C; Azqueta C; Llucia M; Garcia J; Granena A
AUTHOR ADDRESS: Pahissa 13, 08190 St. Cugat del Valles, Barcelona, Spain** Spain
JOURNAL: Bone Marrow Transplantation 18 (5): p879-884 1996 1996
ISSN: 0268-3369
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Seventeen patients with Philadelphia (Ph) chromosome-positive chronic myeloid leukemia (CML) were treated with the ICE regimen plus G-CSF with the aim of mobilizing and collecting Ph-negative peripheral stem cells (PSC) in the setting of an autotransplant program. Fifteen patients had CML in first chronic phase (CP), and two in accelerated phase (AP). Three patients had been previously treated with interferon-alpha 2a (IFN). Twelve patients underwent leukaphereses and a mean of 4.7 times 10-8/kg mononuclear cells were obtained. Four CP patients did not show a significant mobilization peak of CD34+ cells and leukapheresis was not performed; finally, one patient died before apheresis could be performed. Six of the 12 who underwent leukaphereses obtained more than 1.0 times 10-6/kg CD34+ cells. Eight of the 12 mobilized patients (67%) obtained a major cytogenetic response, including two complete and six partial; in the remaining four patients minimal or absent cytogenetic responses were observed. A higher rate of Ph purging was obtained in patients mobilized early or showing residual Ph-negative cells before mobilization, even if they were in AP. Infectious complications were frequent with a 38% rate of bacteremia recorded and one case of pulmonary aspergillosis resulting in a toxicity similar to that occurring in acute myeloid leukemia-induction chemotherapy. The ICE regimen can promote 'in vivo' purging of the Ph+ cells in 67% of CML mobilized patients (8/12). Failure of mobilization occurs in 65% of patients (11/%17%), mainly because of poor CD34+ cell yield.

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DIALOG(R)File 5:Biosis Previews(R)

0010456135 BIOSIS NO.: 199699090195
Treatment of adult metastatic soft-tissue sarcoma with doxorubicin/ifosfamide: Better hematologic tolerance by G-CSF?
AUTHOR: Weh H J (Reprint); De Wit M; Zornig C; Hossfeld D K
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JOURNAL: Onkologie 19 (2): p159-162 1996 1996
ISSN: 0378-584X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: The combination of doxorubicin/ifosfamide is an effective chemotherapy regimen in metastatic soft-tissue sarcomas (STS), generally resulting in remission rates between 30 and 40%. A serious disadvantage of the combination are severe side effects, notably hematotoxicity, often leading to potentially life-threatening infectious complications due to leukopenia. Patients and Methods: Between May 1992 and October 1995, 45 previously untreated patients with advanced/ metastatic STS were treated every 3 weeks with a combination of doxorubicin 30 mg/m-2 on days 1 and 2 and ifosfamide 3 g/m-2 on days 1-3. The first course of chemotherapy was given without G-CSF support. When IV degree leukopenia or fever gt 38 degree C after any course of chemotherapy developed, 5 mu-g/kg G-CSF was administered s.c. on days 4-12 after all subsequent courses. Results: Treatment resulted in severe hematotoxicity. All patients developed at least once III/IV degree leukopenia and 33% developed III/IV degree thrombocytopenia. The 167 courses of chemotherapy were followed by 33 (20%) episodes of fever gt 38 degree C. Particularly the first cycle led to %17% (38%) IV degree leukopenia and febrile events. In 29/45 patients treatment could only be continued by G-CSF support. Remission rate was 32%. In 15 patients metastasectomy was performed after chemotherapy. In 8/9 thoracotomies and in 2/6 laparotomies complete removal of metastases was possible. Probability of median survival for all patients is 14 months, for those who underwent metastasectomy it is %17% months. Conclusions: The combination of doxorubicin/ifosfamide in the doses used by us is an effective but very hematotoxic regimen in STS and should be administered with G-CSF support. In our opinion, such a toxic chemotherapy should be considered in patients with metastatic STS only when additional therapeutic steps for selected patients are planned, such as metastasectomy or high-dose chemotherapy with peripheral blood stem cell support.

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